51 Approach to Pain in Patients with Central Nervous System Metastases

Thomas Chai, Jennifer Erian, Mihir Joshi, Larry C. Driver, and Dhanalakshmi Koyyalagunta

Introduction

Pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage…" and, therefore, involves more than the mere detection of a (potentially) harmful stimulus by the body (which describes *nociception*). Pain, rather, is a subjective, complex condition affected or modulated by many physiological and psychological factors. In this chapter, we describe briefly first the concept of "pain processing," followed by an overview of the various types of the pain, classified by tissue type. The remainder of this chapter describes select pharmacologic agents used to manage specifically the *neuropathic* component of pain in central nervous system metastases. Evidence to support each specific agent's use in this particular condition will be provided, where available.

T. Chai (✉) · J. Erian · L. C. Driver · D. Koyyalagunta
Department of Pain Medicine, UT MD Anderson Cancer Center, Houston, TX, USA
e-mail: tchai@mdanderson.org

M. Joshi
Department of Physical Medicine & Rehabilitation, Baylor College of Medicine, Houston, TX, USA

An Overview of Pain Processing

Within the body's somatic tissue (muscle, bone, joint, tendon, skin, organs, etc.), specific nerve fiber types of sensory neurons, known as A-Δ (or *A-delta*) and C fibers, have in their peripheral terminals specialized receptors that respond to nociceptive stimuli. These specialized receptors, called *nociceptors*, may be activated by chemical, thermal, and/or mechanical stimuli that reach the nociceptor's high threshold for response. These specific "pain" fibers, with their cell bodies located in dorsal root ganglia (or respective cranial nerve ganglia), travel in peripheral nerves (or cranial nerves V, VII, IX, and X) to synapse with second-order neurons located in the central nervous system (either dorsal horn neurons of the spinal cord or neurons within brainstem nuclei). Release of excitatory neurotransmitters, such as glutamate and aspartate, occurs at these nerve synapses, resulting in travel (and modulation) of the nociceptive signals to higher CNS centers, via ascending projections in various tracts (the spinothalamic tract being an important example). An important supraspinal structure in this ascending system is the thalamus, which receives the nociceptive input and sends projections further to other structures in the brain that influence both the discriminative and affective components of pain.

This entire "nociceptive system" may be modulated at multiple points along the pathway.

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For example, chronic nociceptive input (with resultant release of inflammatory mediators) may sensitize peripheral nociceptors, leading to a lowered threshold for response or an increased responsiveness to normal suprathreshold input (a condition known as *peripheral sensitization*). Repetitive stimulation can also result in lowered thresholds for response or increased suprathreshold response of the second-order, dorsal horn neurons (*central sensitization*) or an increased output: input ratio (referred to as the *wind-up phenomenon*) of these neurons.

In contrast to pain facilitation as described above, modulation of nociceptive signals by certain *descending* supraspinal systems results in inhibitory modulation of pain. Some of the structures associated with this descending inhibitory system include the periaqueductal gray, the serotoninergic raphe nucleus, and the noradrenergic locus ceruleus. These systems influence the dorsal horn neurons of the spinal cord via projections within the dorsolateral funiculus. The endogenous opioid system (endorphins, enkephalins, and dynorphins) also exerts its pain inhibitory effects at both the peripheral and central nervous system levels.

The affective component of pain may significantly influence the patient's perception of the pain experience. Spinal pathways leading to both limbic structures and medial thalamic nuclei provide input to areas of the brain related to affect/emotion. For instance, the anterior cingulate cortex of the brain, and its association with limbic structures, appears to be intimately involved in conferring the emotional aspect to pain, having a role in the sensorimotor, cognitive processing, visceromotor, endocrine outflow, skeletomotor outflow, and other responses to nociceptive stimuli.

Types of Pain

There are various ways by which to classify pain, based on factors such as time (acute, chronic), mechanism (trauma, surgical, etc.), or by tissue type (Table 51.1), among other classification schemes. In this chapter, we describe pain by tissue type, using IASP terminology, as follows:

Table 51.1 Classification of pain type by tissue

Nociceptive pain	Examples
Somatic Visceral	Skin, bone, joints, connective tissue, muscle Lung, liver, esophagus, pancreas, intestines, colon, bladder.
Neuropathic pain	Examples
Central pain Peripheral pain	Brain, spinal cord Cranial nerves, spinal nerves and their branches, ganglia

Nociceptive Pain

There are two main types of nociceptive pain – somatic and visceral. Somatic nociceptive pain is associated with injury to somatic, nonneural tissues. Somatic nociceptors innervate somatic structures such as, but not limited to, the skin, subcutaneous tissue, joint capsules, muscles, ligaments, tendons, fascia, periosteum and endosteum of bone, parietal pleura, and parietal peritoneum. Somatic nociceptive pain is usually localizable by the patient.

Visceral nociceptors innervate thoracic, abdominal, and pelvic viscera, and its surrounding connective tissue/capsule, usually not the organ parenchyma proper. Visceral nociceptors are activated by organ distention, inflammation, and ischemia, rather than stimuli such as cutting, stabbing, or burning. Visceral pain is usually described as poorly localized and may be accompanied by autonomic symptoms. Pain from visceral structures may refer to, and be perceived in, a different area of the body – this is due to the convergence of visceral afferent nociceptive fibers with somatic afferent nociceptive fibers onto the same dorsal horn neurons within a similar segment of the gray matter of the spinal cord.

Neuropathic Pain

Neuropathic pain is "pain caused by a lesion or disease of the somatosensory nervous system," as defined by the IASP. There are two subtypes of neuropathic pain – (1) central and (2) peripheral neuropathic pain. Central neuropathic pain (or

simply "central pain") is a type of neuropathic pain "caused by a lesion or disease of the central somatosensory nervous system," whereas peripheral pain involves the peripheral somatosensory nervous system.

The quality of neuropathic pain is described as a burning, throbbing, electrical-shocking, or "pins and needles." Neuropathic pain can be associated with abnormal sensations, spontaneous or evoked, known as *paresthesias*, or with both unpleasant *and* abnormal sensations, called *dysesthesias*. *Allodynia* is a condition whereby pain is experienced from a normally innocuous stimulus, for instance, light touch.

Select Pharmacologic Agents for Neuropathic Cancer Pain

In this section, we describe the major classes of analgesics used for neuropathic cancer pain, including those caused by CNS metastatic disease. A survey of select agents from each class is described below.

Opioid Analgesics

Opioid analgesics (henceforth referred to simply as *opioids*) are drugs that bind to and assert agonist effects on the opioid receptors of the nervous system. Opioids are considered the gold standard in the management of cancer pain, of all types – neuropathic and nociceptive. Opioids produce analgesic effects but may also result in other potentially unwanted side effects (some of which are described in more detail in subsequent sections of this chapter). For instance, central effects from opioids can produce euphoria, dysphoria, sedation, nausea (through direct effects on the brainstem chemoreceptor trigger zone), cough suppression, and probably the most feared complication – respiratory depression (through direct effects on the brainstem respiratory centers). Peripheral effects of opioids can result in constipation (from slowing of gastrointestinal motility), biliary smooth muscle constriction, urinary retention, and pruritis, among many other effects. Below we discuss select opioid analgesics most commonly prescribed for cancer pain by the Pain Service at the authors' institutions. Evidence of efficacy specifically on neuropathic-type cancer pain in human subjects is provided in this section. Table 51.2 is a sample opioid equianalgesic dosing reference from the authors' institution.

Morphine Sulfate

Morphine is known as the prototypic opioid. It is a full agonist at the *mu*-opioid receptor, which is the predominant analgesic receptor within the nervous system. Morphine is absorbed well orally, but undergoes extensive hepatic first-pass metabolism, and therefore, oral dosages must be increased compared to parenteral doses. Morphine undergoes glucuronidation by the liver, with the resulting major metabolite known as morphine-3-glucuronide (M3G). To a much lesser extent, morphine-6-glucuronide (M6G) is produced, this metabolite being more potent than the parent compound. Excretion of morphine and its byproducts is through the renal route. There is concern, therefore, for using morphine in the

Table 51.2 Equianalgesic dosing table

Opioid	Oral dose (PO)	Parenteral dose (IV)	Conversion factor for changing parenteral opioid to oral opioid	Conversion factor for changing oral opioid to oral morphine
Morphine	15 mg	6 mg	2.5	1
Oxycodone	10 mg	N/A	N/A	1.5
Hydrocodone	15 mg	N/A	N/A	1
Oxymorphone	5 mg	0.5 mg	10	3
Hydromorphone	3 mg	1.5 mg	2	5
Fentanyl	N/A	60 mcg	N/A	Should be managed by clinicians experienced in pain management

Note: Methadone should be initiated and managed by clinicians experienced in pain management
Source: UT MD Anderson Cancer Pain – Adult Practice Algorithm

renal patient population, as active metabolite accumulation could lead to neurotoxic and other significant adverse effects. Morphine is often combined with other agents and adjuvants [1–3] for neuropathic cancer pain, and it is one of the few drugs approved by the United States Food and Drug Administration (FDA) for use in intrathecal drug delivery systems.

Tramadol

Tramadol is a synthetic opioid with dual properties – agonist effects on the *mu*-opioid receptor and norepinephrine/serotonin reuptake inhibition. Tramadol undergoes hepatic metabolism, with one of the active metabolites, desmetramadol, being notable for its much higher affinity for the *mu*-opioid receptor compared to its parent compound. Tramadol and its by-products are excreted renally and also must be used carefully in renally impaired patients. Tramadol was assessed [4] for efficacy, safety, and quality-of-life impact for patients with neuropathic pain in cancer. In this double-blind, placebo-controlled study, patients were randomized to receive either tramadol or placebo. Thirty-six patients were enrolled and equally divided into each study group. Tramadol was given in the treatment arm at 1 mg/kg every 6 hours and increased to 1.5 mg/kg every 6 hours if necessary. The group receiving tramadol showed major improvement in pain intensity, Karnofsky scores, sleep quality, and activities of daily living, compared to the placebo group. In this study, tramadol was concluded to be a therapeutic option to control neuropathic cancer pain and improve quality of life in the cancer patient.

Hydromorphone

Hydromorphone, like morphine, undergoes metabolism by conjugation to form metabolites hydromorphone-3-glucuronide (H3G), predominantly, and 6-glucuronide, which are excreted in the urine. Similarly to the morphine metabolites, these byproducts may also contribute to neurotoxic side effects, requiring caution when prescribing to the renal population. Hydromorphone is considered, mg to mg, about five times more potent than morphine.

Fentanyl

Fentanyl is a synthetic, highly lipophilic opioid, with a potency of roughly 100× that of morphine. Fentanyl has properties of rapid onset and short duration of action and is used commonly in perioperative and intensive care settings. There are various preparations of fentanyl for different routes of administration, including parenteral, transmucosal, transdermal, and spinal. Fentanyl's major metabolite is norfentanyl, which is inactive and thus considered less risky to use in the renally impaired patient population.

N-Methyl-D-Aspartate (NDMA) Antagonists: Methadone and Ketamine

Methadone

Methadone, a synthetic opioid, is an agonist at the *mu*-receptor, but also an antagonist of the N-methyl-D-aspartate (NMDA) receptor, which is implicated in central sensitization/hyperalgesia. Methadone has highly variable pharmacokinetic properties and a long half-life. In addition, methadone is biotransformed hepatically and may be affected by other drugs that inhibit its metabolism; therefore, expert prescribing and monitoring of methadone is necessary to minimize risks of respiratory depression. Methadone is regularly prescribed at the authors' institution for cancer-related neuropathic pain, as there is both anecdotal and scientific evidence [5–7] supporting its use in this condition, particularly when the neuropathic pain is refractory even to high-dose opioids. For example, Sugiyama et al. [8] performed a retrospective study on the effectiveness of changing patients' opioid regimens to methadone for cancer-related neuropathic pain. The Faces Pain Scale (FPS) was used to measure pain intensity and pain relief. Twenty-eight patients on other potent opioids were changed to methadone, and 78.6% of those patients, within 2 weeks, had a significant reduction in their mean FPS score, and 12 out of 17 patients either reduced or discontinued entirely adjuvant analgesics.

Ketamine

Ketamine is an anesthetic that has analgesic and dissociative properties. Its analgesic property is

thought to be related to its antagonism of the NMDA receptor. Although randomized clinical trials show little efficacy for ketamine in managing cancer pain, there are a number of case series and open-label studies that show benefit [9]. For instance, Mercadante et al. [10] published a case report on administration of ketamine as a subcutaneous infusion in a patient who experienced opioid-resistant neuropathic cancer pain, with dramatic reduction in opioid requirement and continued relief after 13 months with treatment, despite progression of disease.

Ketamine is utilized in the authors' pain clinic practice as an intravenous infusion at 0.5 mg/kg, over a one-hour duration; however, there is no consensus as to the optimal protocol, and, consequently, there exist many parenteral ketamine protocols for treating unremitting cancer pain [11–13].

Opioid Safety Considerations

In this section, we describe some of the most pressing or concerning side effect and safety issues associated with opioid prescribing. As the use of opioid medications for pain management has increased steadily over the past decades, the incidence of opioid-related deaths has tracked closely with this trend, as reported by the Center for Disease Control and Prevention (CDC). Initial public acceptance of opioid medications as generally safe agents has given way to an increased awareness of the risks associated with their use. Additionally, increased prescription of opioid medications has increased the incidence of diversion and misuse. Indeed, the Center for Medicare and Medicaid Services (CMS) has declared the opioid misuse epidemic a public health emergency, and many policies are in place to address this opioid crisis here in the United States. For instance, the CDC has published guidelines on opioid therapy for chronic pain. (Notably, the CDC states that their chronic opioid prescribing guidelines are not applicable for patients on active cancer treatment, palliative care, or end-of-life care.)

Opioid medications remain a major component of the treatment of cancer pain, due to the wide range of available agents and routes, availability of immediate- and extended-release formulations, and efficacy in many types of pain. These benefits must be carefully considered against the side effect profile common to most opioid agents, as well as the significant risk of disorders related to opioid use. Awareness of the side effects and safety considerations involved in opioid therapy, as well as a proactive approach to addressing them, are imperative in effective risk management for patients using opioid medications.

Cognitive Impairment

Concurrent use of opioids with sedating agents may increase the risk of cognitive impairment. Because cognitive impairment can present either in opioid overdose or in the course of regular opioid use, it is important to readily identify whether a patient may indeed be in overdose – a potentially fatal situation. For example, *rapidly* declining cognitive status after opioid administration is more concerning for overdose and warrants prompt evaluation. In cases where cognitive impairment seems to be linked to regular opioid use and has a more gradual onset, there are a few strategies available for the prescribing provider. The first is to consider dose reduction if analgesia is sufficient at the current dose; this is done with the knowledge that pain may worsen. If dose reduction is not a viable option, consider opioid rotation or dose reduction alongside the addition of an adjuvant analgesic (next section of this chapter).

Opioid Overdose

The 2017 data from the National Institutes of Health demonstrate a continued trend of increasing opioid overdose deaths, with opioid pain relievers accounting for approximately 40% of total opioid overdose deaths. Though the great majority of these events involve diversion, co-ingestion, or misuse, prescribers should be aware of the risk and available treatment.

Co-ingestion with sedating agents, including but not limited to benzodiazepines and alcohol, dramatically increases the risk of respiratory depression. Additionally, any condition (pulmonary disease/compromise, sleep apnea, stroke history, brain injury) or prescription medication that increases the patient's risk of respiratory depression must be weighed when initiating or escalating opioid therapy. For example, the FDA has in place a box warning as of 2016 regarding the combined use of opioids and benzodiazepines, due to evidence of the combined increased risk of respiratory depression and death when these agents are used in conjunction. Prescribers should counsel patients on this risk when initiating opioid therapy for a patient already on benzodiazepines or those with comorbid conditions. A low starting dose and slow drug titration can help minimize the risk of overdose and respiratory depression.

Opioid misuse can stem from the intentional therapeutic use of the opioid, but in an inappropriate way. Abuse occurs when patients use opioids for intentional nontherapeutic use to achieve a desirable effect. Patients on daily opioid medication must be counseled therefore to take their medication strictly as prescribed. Daily opioid use can lead to the development of physiologic tolerance, a condition of diminishing analgesic effect over time. Rapid development of tolerance is a phenomenon known as *tachyphylaxis*. Another concept, called the opioid-tolerant state, is defined as the state whereby a patient is taking at least 60 mg daily of oral morphine or its equivalent, for at least 1 week. This state is in contrast to the opioid-naive state, where the patient has no regular exposure to opioids, and to the opioid *non*-tolerant state, where the patient is using opioids regularly, but not to the amount sufficient to meet the criteria for the opioid-tolerant state. A period of abstinence can lead to the loss of the opioid-tolerant state, which can result in unintentional overdose when the patient attempts to resume their opioid therapy. Therefore, it is advisable for physicians to check with their patients at every appointment to ensure they understand the importance of taking their medication as directed. If a patient abruptly discontinues opioid therapy, he/she may experience a withdrawal syndrome, resulting in an "autonomic arousal" described as a limited period of irritability, agitation, lacrimation, yawning, abdominal cramping, and loose stools, among other unpleasant sensations.

Despite preventative measures, opioid overdoses continue to occur at increasing rates, year after year, in the United States. As part of a broader harm-reduction initiative, the FDA approved the opioid antagonist naloxone (trade name Narcan) in 1971 for treatment of opioid overdose. Initially available only as intravenous or intramuscular injections, naloxone is now available as a subcutaneous injectable, intramuscular auto-injector, and intranasal spray. The latter is seeing increased use as an effective rescue medication deployed by first responders and community bystanders to reverse opioid overdose, and its prescribing is encouraged under the "Surgeon General's Advisory on Naloxone and Opioid Overdose," by the current US Surgeon General, Dr. Jerome Adams, for patients who are at higher risk for opioid-use disorders. Increasingly, physicians are co-prescribing naloxone with opioids for patients on nominally high doses, patients with preexisting risk factors for respiratory depression, or patients where the risk of opioid overdose is felt to be significant [14, 15]. This measure was added to the CDC's 2016 prescribing guidelines for opioid therapy as a harm-reduction strategy worthy of consideration when initiating or escalating opioid therapy. Naloxone, available in easily administered intranasal or intramuscular forms without a prescription in 48 states, acts within minutes to displace opioid agents from central *mu*-receptors. Patients who are at higher risk for an overdose event should be educated on the use of naloxone, and more importantly so should any individual who will be with the patient on a regular basis. Like intramuscular epinephrine auto-injectors for patients with anaphylaxis, naloxone will often be administered to the patient by someone who is with them around the time of overdose.

Naloxone has proven to be extremely efficacious as a rescue agent, with a 2014 meta-analysis [16] demonstrating an Odds Ratio (OR) 8.58 of

increased recovery from opioid overdose when naloxone is administered. Its pharmacokinetic profile allows for rapid decoupling of opioid agents from the *mu*-receptor, but it also dissociates itself from the *mu*-receptor within minutes. Depending on the location and response time of emergency services, it may be necessary to administer multiple successive doses of naloxone to maintain respiratory function until first responders arrive.

Diversion

Diversion, either intentional or unintentional, is a major concern for physicians, patients, the healthcare system, and law enforcement agencies. A landmark 5-year national study of diversion revealed over 64,000 reported cases [17]. Due to acknowledged study shortcomings, and Substance Abuse and Mental Health Administration (SAMHSA) survey data showing abuse rates of hydrocodone and oxycodone measuring 17.7 million and 13.6 million individuals, respectively [18, 19], there is good reason to suspect the actual rate of diversion is far higher.

Several trends have emerged in diversion and prescription opioid abuse. The first is that, overall, immediate-release (IR) formulations are diverted and abused at higher rates than extended-release (ER) formulations. The second is that an initial preponderance of prescription opioid abuse in rural communities, thought to be secondary to higher availability of street drugs in urban communities, has begun to level off. Prescription drug abuse is seen now at high levels in urban, suburban, and rural settings across all socioeconomic strata. The third is the importance of cultural and employment differences between rural and non-rural settings; in communities where the majority of employed adults perform manual labor (e.g., coal mining, farming, logging, fishing), the incidence of occupation-related pain is higher. Thus, the prevalence of pain and the prevalence of pain medication prescribing are higher on a per capita basis. The widespread nature of prescription opioid utilization in these communities is thus more commonly accepted as a part of life, as are the dependence and abuse that follow. The fourth, and perhaps most important, is the lack of consensus on the actual mechanics of opioid diversion. SAMHSA data, which rely on self-reporting, show that 75% of opioid abusers obtained medications from a family member or friend. Increased activity at all levels of law enforcement to counter street and internet sales of prescription pain medication has not addressed, therefore, what may be the most common route of opioid diversion. While opioid medications continue to maintain a high street price, making them a lucrative option for patients in financial strain, the data suggest most diversion is not transactional. Diversion from friends and family, whether solicited or unsolicited, seemingly constitutes the major access route for individuals seeking unprescribed opioids. That said, hard data on diverting mechanisms are scarce due to a variety of social and political factors, as well as limits in effective data collection.

Regardless of routes to diversion, the fact agreed upon most commonly is that the major source for diverted opioids is patients who receive prescriptions for opioids. The prescribing physician, then, plays a role in reducing diversion. This fact is reflected in increased scrutiny by federal agencies of physicians' prescribing practices, as well as pharmacies that dispense opioids. Here is a selection of some tools physicians can utilize to reduce the risk of involvement in diversion:

- *Pain Contract:* In its most basic form, a pain contract will bind the patient to three rules. First, that their pain physician will be his/her only source of opioid prescriptions. Second, that he/she will only use one pharmacy to fill his/her prescriptions. Third, that he/she will be the only ones to use his/her prescribed opioid medications. Additional language may include a promise not to miss appointments or use other sedatives, consent to random drug screens at office visits, or restrictions on refills in the event of lost or stolen medication. This document, signed by the patient and countersigned by the prescribing physician, acts as a code of conduct for both parties and defines the terms under which the prescribing physi-

cian will continue to prescribe opioids to the patient. The contract is enforceable to the extent that the physician is willing to stop seeing a patient who violates its terms.

- *Drug Screen:* Used in conjunction with a contract, random drug screens, most commonly using hair, urine, or saliva, are a way to ensure a patient is taking prescribed medications and no other agents of concern [20, 21]. Older drug tests could only detect opioids generally, while newer tests can detect active drug and metabolites for a variety of commercially available and illicit agents. If a patient is diverting their prescribed medication, or if they are using any prescribed agents in conjunction, a drug screen will be able to reveal this.
- *Prescription Drug Monitoring Program (PDMP):* PDMP systems, which have been developed in North America, Australia, and some European countries, have allowed an increased degree of prescription monitoring. Patients are entered into a database by pharmacies, listing their prescribed controlled agents, dosing, prescriber information, and filling pharmacy. These programs were started in an effort to reduce "doctor shopping," whereby patients would go to multiple physicians to get opioid prescriptions, filling them at multiple pharmacies to avoid raising suspicion. Where available, PDMP data should be reviewed at every patient visit to ensure fidelity with single-prescriber and single-pharmacy rules. If any discrepancies are revealed, they should be discussed with the patient.

Opioid medications, owing to their effectiveness against multiple pain mechanisms, are widely used in the treatment of cancer pain. Effective pain management, in turn, improves quality of life for patients with cancer and also increases their ability to continue treatment. The safety considerations involved in opioid use are significant, and merit constant surveillance by prescribing physicians to ensure patients are using their medications appropriately with minimal adverse effects.

Adjuvant Analgesics

In this section, we describe some of the most commonly prescribed adjuvants for neuropathic pain. Adjuvant analgesics are drugs that with primary indications not related to pain but are found to be useful for their pain-relieving effects. The specific adjuvants detailed here are ones with historical benefit for a variety of neuropathic pain conditions, and many belong to the class of medications used to treat seizures and depression. In fact, anticonvulsants and antidepressants are considered first-line agents for neuropathic pain in cancer, often used in combination with opioids. Use of these adjuvants can reduce the patient need for opioids, an effect called *opioid-sparing*.

Anticonvulsants

Gabapentin and Pregabalin

The anticonvulsant drugs most commonly employed for neuropathic cancer pain are gabapentin and pregabalin. These two drugs have similar pharmacodynamic properties, in that they both inhibit voltage-gated calcium channels, through blockade of the α_{-2}/Δ_{-1} subunit of these channels, which are upregulated in pain states. Both gabapentin and pregabalin are structurally similar to gamma-amino-butyric acid (GABA); however, they are not ligands for the GABA receptor. These drugs are not metabolized, and drug clearance is through the renal route (urine); thus, dose adjustment is necessary in those with renal insufficiency. The most common side effects reported for these "gabapentinoids" include dizziness, drowsiness, weight change (gain), and edema of the hands and feet.

Several studies support the effectiveness of gabapentinoids for neuropathic cancer-related pain. For example, in a prospective, open-label study, Ross et al. [22] studied gabapentin effectiveness in two parallel groups – 25 patients in the first group had cancer-treatment-related neuropathic pain, while 37 patients, assigned to the other group, had tumor-related neuropathic pain. Gabapentin dosage was titrated to 1800 mg/day for patients in both groups. Pain scores per the

modified Brief Pain Inventory (BPI) were assessed as the primary outcome measure, and the results of the study showed a significant reduction in "worst," "average," and "current" BPI pain scores, but not the "least" score. Of the total patients, 45.2% achieved a minimum of one-third reduction in the pain score. The authors of this study concluded that gabapentin was indeed effective in the treatment of cancer-related neuropathic pain.

Caraceni et al. [23] performed a multicenter, randomized, double-blind, placebo-controlled, parallel-design trial to determine the analgesic effect of adding gabapentin to opioid therapy for managing neuropathic cancer pain. A total of 121 patients were enrolled in the study. Gabapentin was titrated to 1800 mg/day while patients remained on stable opioid therapy. Average daily pain was measured by Numerical Rating Scale (NRS) score, and the whole follow-up average pain score was used as the primary outcome measure. A total of 79 patients received gabapentin and 58 completed the study; 41 patients received placebo, of which 31 completed the study. Analysis showed a significant difference of average pain intensity between the gabapentin group and placebo group, supporting the effectiveness of gabapentin in improving analgesia in neuropathic pain cancer patients using opioids.

In a similar study [3], the efficacy and safety of pregabalin were evaluated in neuropathic cancer pain patients who were using morphine. Forty patients were randomized into two groups: the first group received pregabalin plus oral morphine in Phase I and then placebo plus oral morphine in Phase II, while the latter group received the opposite in each phase. There was a 1-week washout period between phases. The primary outcome measure was reduction in oral morphine dose. Results showed that there was a significant reduction in the mean minimal effective dose of morphine during treatment with pregabalin. The authors concluded that pregabalin enhanced the efficacy of oral morphine, while also reducing opioid dose-related side effects, in cancer patients with neuropathic pain.

In another study [24], low-dose gabapentin was studied in combination with imipramine for neuropathic cancer pain. Fifty-two patients were assigned into one of four groups. Those in group 1 were administered both gabapentin 200 mg and imipramine 10 mg every 12 hours; group 2, gabapentin 200 mg every 12 hours; group 3, gabapentin 400 mg every 12 hours; and group 4, imipramine 10 mg every 12 hours. Results showed that the low-dose gabapentin–imipramine combination significantly reduced total pain score, as well as daily paroxysmal pain episodes.

Pregabalin was compared to opioids for both safety and efficacy in treating neuropathic cancer pain in a prospective, head-to-head, randomized, open-label study [25]. A total of 120 patients were randomized into two groups, receiving increasing doses of either oral pregabalin or transdermal fentanyl. The main outcome measure was pain score by VAS. A significantly higher proportion of patients had at least 30% reduction in pain score, compared to the fentanyl group, and the percentage mean change (decrease) from pain baseline was significantly different for pregabalin versus fentanyl. Secondary measures of patient-reported satisfaction were also more frequent in the pregabalin-treated group, and adverse events and treatment discontinuation were higher in the fentanyl group. This study concluded that the use of adjuvants, like pregabalin, could lead to better neuropathic pain control and to opioid sparing effects.

A post hoc analysis [26] of pregabalin versus non-pregabalin-treated patients with neuropathic cancer pain in a 2-month multicenter, prospective, epidemiologic study showed a higher satisfaction rate, decreased benzodiazepine use, and decreased total pain intensity and interference in the Brief Pain Inventory for those patients treated with pregabalin polytherapy, compared to the non-pregabalin treatment group. The study authors concluded that the addition of more specific drugs that target neuropathic pain in affected patients provides more treatment satisfaction and better pain- and pain interference-related outcomes.

Carbamazepine and Oxcarbazepine

Carbamazepine and its structural derivative, oxcarbazepine, are sodium channel blockers that

appear to selectively inhibit active A-Δ and C nociceptive fibers, blocking both peripheral and central pathways for pain. Although the literature is sparse in describing their effects on cancer pain, these drugs are well established in managing other chronic pain conditions with a neuropathic component, such as trigeminal neuralgia [27] and various forms of peripheral neuropathy [28, 29]. Oxcarbazepine is considered to have a more favorable safety profile, with less risk for hepatic or hematologic adverse reactions, compared to carbamazepine.

Antidepressants

Duloxetine

Duloxetine is a serotonin- and norepinephrine-reuptake inhibitor (SNRI) antidepressant, approved by the US FDA to treat depression, generalized anxiety disorder, and pain associated with various conditions, such as painful diabetic peripheral neuropathy, fibromyalgia, and chronic, multisite musculoskeletal pains. In the cancer patient population, duloxetine has been used to manage chemotherapy-induced peripheral neuropathy pain [30, 31] and joint pains from aromatase inhibitor therapy [32, 33]. Although less well supported, duloxetine has been routinely used also to manage cancer pain with a neuropathic component. In a small retrospective pilot study, Matsuoka et al. [34] assessed the effectiveness of duloxetine in patients with cancer-related neuropathic pain refractory to opioids and gabapentinoids, finding it to be effective in reducing pain scores in 7 of 15 patients. The same authors have underway a prospective, randomized phase III study [35] to further establish evidence to support duloxetine use in this setting.

Amitriptyline

Amitriptyline is a tricyclic antidepressant, with evidence supporting its efficacy as an adjuvant for neuropathic pain in conditions such as central pain related to stroke and spinal cord injuries, as well as peripheral neuropathic pain related to diabetes, chemotherapy, and postherpetic neuralgia, among many other neuropathic pain conditions. There are few, small studies supporting its use for neuropathic cancer pain. For instance, a study by Banaerjee et al. [36] compared the efficacy and safety of amitriptyline versus gabapentin as a co-analgesic for patients receiving opioids to manage cancer-related neuropathic pain. Eighty-eight patients with neuropathic pain in malignancy were randomly assigned to two groups. The first group received gabapentin and tramadol, while the second group received amitriptyline and tramadol. At 6 months, there was a decline in Visual Analogue Scale (VAS) scores from baseline in both treatment groups, without any statistically significant difference between groups. The authors of the study concluded that amitriptyline could be an appropriate alternative to gabapentin for managing neuropathic pain from cancer.

In a prospective randomized study, Mishra et al. [37] compared the efficacy of amitriptyline, gabapentin, and pregabalin for neuropathic cancer pain. A total of 120 patients with neuropathic cancer pain were enrolled and divided into four different groups: amitriptyline group, gabapentin group, pregabalin group, and placebo group. A significant reduction in VAS scores were seen in all groups, with the authors concluding that all of the anti-neuropathic drugs studied demonstrated effect in relieving cancer-related neuropathic pain.

Topical Agents

Lidocaine

Lidocaine is a local anesthetic of the amide type. Lidocaine inhibits voltage-gated sodium channels within nerve cell membranes, preventing depolarization and, therefore, action potential generation. Lidocaine is available in topical form, and it can be helpful in relieving malignant neuropathic pain. Lopez Ramirez [38] conducted a study aimed to evaluate the efficacy of lidocaine 5% patch for focal neuropathic pain in patients with or without cancer. Fifteen patients were recruited. Six of the fifteen patients had cancer-related neuropathic pain. Eight out of the 15 patients treated reported a potent analgesic effect, and four patients reported partial analgesia.

Fleming and O'Connor [39] retrospectively audited the use of lidocaine patch 5% in a comprehensive cancer center. Among the 97 patients prescribed the patch, 26 were for persistent postsurgical neuropathic pain, 24 were for postherpetic neuralgia, and 18 were for cancer-related neuropathic pain. Allodynia was a feature in 60% of these patients, and analgesic efficacy in those with allodynia was "potent" in 35%, 38%, 39%, respectively.

Kern et al. [40] performed a retrospective analysis of 68 case reports regarding 5% lidocaine medicated plaster for cancer pain with a neuropathic component or for trigeminal neuropathic pain. The plaster was found most helpful for surgical- or chemotherapy-related neuropathic pain, with at least 50% of those using the plaster able to dose-reduce systemic analgesics. In trigeminal neuralgia, potential predictors of response to lidocaine plaster were found to be hyperalgesia, allodynia, continuous pain, among others.

Capsaicin

Capsaicin is the substance that gives chili peppers the characteristic burning sensation with tissue contact. Capsaicin, along with heat, acid, and other ligands, binds to transient receptor potential vanilloid subtype 1 (TrpV1), a cation receptor expressed on the peripheral and central terminals of nociceptive neurons. Prolonged capsaicin exposure is thought to result in a paradoxical desensitization of TrpV1, with subsequent analgesic effect. Although well studied for nonmalignant neuropathic pain conditions [41, 42], capsaicin has limited evidence in the cancer neuropathic pain patient. One study, however, of chronic postsurgical neuropathic pain in 99 cancer survivors [43] involved an 8-week application of 0.075% capsaicin cream four times daily to the affected painful area, followed by 8 weeks of placebo cream application, or vice versa. The capsaicin cream arm of treatment had a significant reduction in pain compared to placebo. The capsaicin treatment arm was associated, however, with significantly more skin burning and redness, but treatment arm discontinuation was similar in both groups. At the end of the study, participants were asked which treatment arm was most beneficial – 60% chose the capsaicin arm, 18% chose the placebo arm, and 22% chose neither. The authors of the study concluded that topical capsaicin cream significantly decreased postsurgical neuropathic pain in cancer patients and was preferred by patients over placebo by a 3:1 margin.

Conclusion

Cancer-related neuropathic pain, such as from CNS metastases, can be a challenging condition to manage. A multidisciplinary strategy, including potential interventional pain management strategies discussed elsewhere in this book, is essential to optimize patient outcomes. Providers should consider not only opioid drugs but also other adjuvants with analgesic properties such as antidepressants, anticonvulsants, and local anesthetic classes, among others.

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