Cancer Pain Management
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Upon successful completion of this continuing education activity, the pharmacist should be able to:
1. Identify different types of cancer pain and their potential causes.
2. Compare and contrast the non-opioids used in cancer pain management and list precautions for the use of NSAIDs in cancer patients.
3. List one major disadvantage to the use of weak opioids in cancer pain management.
4. Compare and contrast strong opioid agents used in cancer pain management, including potential advantages and disadvantages for each strong opioid.
5. List the ideal characteristics of an opioid agent utilized for breakthrough pain.
6. Recommend appropriate treatment options for common opioid side effects, including but not limited to constipation, nausea, vomiting, itching and respiratory depression.
7. Compare and contrast commonly used agents for neuropathic cancer pain management, including potential advantages and disadvantages for each agent.

INTRODUCTION
Pain is usually the first sign of malignancy in most cancer patients. However in certain types of cancer, some patients may experience little or no pain. Overall, about 50 percent of patients feel pain at the time of diagnosis, and about 75 percent feel pain in advanced stages. Pain is also seen in cancer survivors, mostly due to neuropathy related to complications from surgery and chemotherapy. According to the International Association for the Study of Pain (IASP), the prevalence of pain varies according to the type and location of the tumor. For example, the prevalence of pain in patients with cancer in the head and neck region is 67–91 percent, and in those with breast cancer is 40–89 percent. Surgery, as part of cancer treatment, and chemotherapy often cause neuropathic pain in cancer survivors. Apart from the underlying pathophysiology of cancer-induced pain, other factors such as fatigue, nausea, constipation and impaired mental function also exacerbate perception of pain.

With currently available pharmacological agents, and with some complementary therapies, cancer pain can be effectively treated in many patients. The World Health Organization (WHO) estimates more than 80 percent of the world’s population does not receive adequate treatment for moderate to severe pain due to various causes. Prevalence of under-treated cancer pain in developing countries is also very high, mostly due to the delayed
diagnosis of cancer and also due to the taboo against use of opioids. Adequate pain control enhances the quality of life in these cancer patients, and brings comfort to those who are terminally ill. Given the availability of several pain relieving strategies, cancer patients living or dying with unrelieved pain is not justified. The major barriers for inadequate treatment of cancer pain are related to the patients, providers, and the health care system of the country. Patient factors that contribute to the inadequate treatment of pain include fear of side effects, fear of dependence or addiction, fear of distracting providers from treating the underlying cancer and belief that an increase in pain is indicative of progression in the disease condition. Fortunately, there are several support programs available for patients to overcome these barriers. Health care professionals may also be barriers. For example, inadequate pain assessment by the provider and concerns regarding legal issues of prescribing and dispensing narcotic analgesics contribute to inadequate treatment. Health care system structures also pose problems for adequate treatment of pain; lack of insurance coverage can result in inadequate pain treatment. It should be noted, however, that the use of several drugs available for treating pain in cancer patients is truly limited by their adverse effects, particularly their abuse, misuse, and addiction potential. More potent analgesic agents with minimal undesirable side effects are desperately needed for the treatment of pain cancer patients.

The pathophysiology of cancer pain is complex when compared to other types of pain, mostly because of the multitude of factors involved such as type, size and location of the tumor and metastases. Inconsistent pain presentations, mostly due to differences in locations and severity of tumor growth, in certain common types of cancer such as breast cancer, lung cancer or prostate cancer makes the study of pain generation mechanisms even more challenging. Investigators have identified some key mediators of pain in various types of cancer, mentioned in the following paragraph. The pain that is experienced by cancer patients is due to changes that happen at the cellular, tissue or systemic levels that occur during and after tumor generation. Cancer patients suffer from two major types of physical pain: nociceptive pain due to the activation of nociceptors in the affected area, and neuropathic pain due to nerve damage by tumors or due to chemotherapy.

One of the most common causes of nociceptive pain in cancer is tumor enlargement. When a tumor grows, it exerts mechanical pressure on nociceptors in the nerve terminals. Another source of nociceptive pain is the release of inflammatory and pro-hyperalgesic mediators by the tumor cells, such as endothelin, bradykinin, prostaglandins, and tumor necrosis factor alpha (TNF-α). These mediators either directly activate nociceptors, causing pain sensation or sensitize nociceptors causing lower pain threshold. It is known that the pH in tumor tissue is lower than normal tissues (more protons), and this low pH can activate certain nociceptive channels. Activation of these receptors also causes pain. In cancer of the viscera, stretching of hollow viscera, distortion of the capsule of solid organs, inflammation of the mucosa, and ischemia or necrosis activate visceral nociceptors leading to generation of visceral pain. Rapid weight loss, muscle hypercatabolism, immobilization, or increased muscular tension that is commonly seen in cancer patients can cause muscular pain.

Metastasis is another common cause of pain in cancer. Although bone is not a vital organ, many common tumors metastasize to multiple bones at the same time. A variety of cells, including tumor cells and stromal cells (including inflammatory/immune cells, osteoclasts, and osteoblasts) mediate bone cancer pain. Nociceptors that innervate the bone use several different types of receptors to detect and transmit noxious stimuli that are produced by cancer cells, tumor-associated immune cells, or other aspects of the tumor microenvironment. Bone pain can be debilitating as the pain severity often worsens with movement, thus potentially limiting patient functionality.

Breakthrough pain, defined as a transient flare of pain that occurs on a background of relatively well-controlled baseline pain is prevalent in cancer patients. This may be due to a number of causes, such as bony metastases causing pain on movement, or increased pressure in the tumor due to movement. The
movement-evoked breakthrough pain in cancer patients is partially due to the tumor-induced loss of the mechanical strength and stability of the tumor-bearing bone so that normally innocuous mechanical stress can now produce distortion of the nerves in the bone.

Neuropathic pain is commonly seen in cancer patients, especially those with a long-term prognosis. Cause of neuropathic pain in cancer is mainly due to damaged nerve endings at the tumor site from enlargement of tumors. Tumor infiltration in nerve plexuses and damage to nerve tissue can also cause neuropathic pain. Some chemotherapy agents cause nerve damage and peripheral neuropathy. Chemotherapy-associated neuropathy arises due to different mechanisms, including disruption of nerve function and triggering release of cytokines, which results in degeneration of sensory neurons and sensitization of primary nociceptive afferents.

**MANAGEMENT OF NOCICEPTIVE PAIN IN CANCER PATIENTS**

Cancer patients experience pain brought on by either the treatment or the cancer itself. The pain duration experienced by cancer patients can be either acute or chronic pain, with chronic pain being more common. Chronic pain has no definitive onset and the patient does not always appear to be in acute distress. Acute pain has a definitive onset, only lasts a short period of time, and patients tend to show observable signs of pain.

Many variables help clinicians determine an appropriate treatment regimen for pain patients, with pain intensity being a very important determining factor. Evaluation of pain intensity may be accomplished using one of the many different screening options available, the most common of which is a numerical scale with 0 being no pain and 10 being the worst pain experienced. The Wong-Baker faces pain rating scale allows an alert and conscious patient assesses their pain by choosing from six different drawn facial expressions numbered 0, 2, 4, 6, 8, 10. A visual analogue scale prompts the patient to pick a point on a continuous line from 0–10 to describe the level of pain.

Patients who cannot express themselves or understand other pain scales, such as small children and patients with cognitive impairment, can be assessed by healthcare workers using the FLACC scale. Health care workers observe the Face, Legs, Activity, Cry and Consolability of the patient to assign each 0–2 points; up to 10 total points. Values based on the 0–10 numbering system can be classified as 0 being no pain, 1–3 being mild pain, 4–6 as moderate pain, and 7–10 as severe pain. Children and the elderly are more likely to be undertreated for pain because they cannot effectively communicate their pain intensity. In these cases it is important for a patient to have a caregiver who can identify the patient’s needs or changes in behavior to help determine the amount of pain being experienced. Pain may be identified by changes in eating habits, agitation, crying, acting uncooperative, and being inconsolable. Another practical disadvantage to these tools is lack of past experience with pain. Many patients have never had a previous severe pain episode to be able to relate to “worst pain experienced.” Thus it is often good practice to qualify worst pain experienced, by comparing to an extreme pain scenario such as a broken femur. This may help clinicians to minimize over-aggressive treatment of patients unknowingly reporting high pain intensity numbers.

Another important consideration when determining a patient’s treatment regimen is the patient’s current or past experience with medications. Of importance is a patient’s tolerance of medications, particularly opioids. Opioid-tolerant patients are those who have received daily opioid analgesics for one week or longer, and doses of at least: 60 mg oral morphine/day, 25 mcg transdermal fentanyl/hour, 30 mg oral oxycodone/day, 8 mg oral hydromorphone/day, 25 mg oral oxymorphone/day, or an equianalgesic dose of another opioid. An opioid naïve patient has not built up a tolerance to opioid therapy, and therefore an opioid naïve patient requiring opioid therapy should be started on low doses and titrated very carefully. If the patient is experiencing mild pain, a non-opioid medication should be considered first-line. For moderate pain a combination opioid product, such as hydrocodone-acetaminophen, may be the best choice. A low dose pure opioid could also be considered in a patient with moderate pain or when the use of acetaminophen or ibuprofen
is not desired. It is important to start the patient on a low dose and titrate up slowly as needed and keep in mind daily acetaminophen limits when applicable. In severe or uncontrolled pain, a pure opioid often is required along with frequent assessment of the patient, as rapid titration may be necessary to manage the patient’s pain. After initiation of a pure opioid, if the patient’s pain is still moderate or not adequately controlled, consider titrating up their scheduled and as-needed opioid regimens by approximately 25–50 percent. If the patient’s pain is still severe after the initiation of a pure opioid, it may be necessary to titrate up the doses by approximately 50–100 percent or reevaluate the need for an alternative opioid regimen.

WHO has developed a three-step cancer pain relief ladder outlining proper procedure for the overall use of varying strengths of opioids in cancer pain treatment. In all of these steps adjuvant therapy and breakthrough pain regimens should be considered as well.

**STEP 1**: When pain first occurs or is mild, non-opioid therapy should be administered.

**STEP 2**: If pain continues and is now mild-moderate, a weak opioid or opioid combination product should be administered and non-opioid therapy may be continued if desired.

**STEP 3**: If pain continues and is now moderate to severe, a pure (strong) opioid should be administered until the patient is pain free. Continuation of non-opioid therapy may be considered.

Opioid therapy should be administered on a regular schedule around the clock to optimize pain relief in patients with moderate to severe pain. Onset of action, duration of action, half-life, and side effects should all be taken into consideration when selecting the best on analgesic regimen for a patient.

**NON-OPIOIDS**

Non-opioid therapy has a well-established role in the treatment of cancer pain. Non-opioids can be used an initial monotherapy for mild cancer pain, as they are effective for mild pain and well tolerated when used at appropriate doses. Approximately 27 percent of cancer patients will have adequate pain relief from non-opioid analgesic agents during the course of their disease. A disadvantage to these medications is an analgesic ceiling effect and therefore a maximum dose per 24 hours. Since these medications have an analgesic ceiling effect and a risk for serious adverse effects at higher doses, they should be used in combination with opioids if used for moderate to severe cancer pain. Acetaminophen works as an analgesic by inhibiting prostaglandin synthesis and has minimal anti-inflammatory effects. Acetaminophen causes fewer adverse reactions compared to non-steroidal anti-inflammatory drugs (NSAIDs), but high doses lead to serious hepatic toxicity. It is recommended to have a maximum daily dose of 4 g/24 hours, and possibly even lower for patients with liver disease. The Food and Drug Administration (FDA) is currently considering recommending the daily maximum dose for chronic use be limited to 3 g/24 hours. NSAIDs, on the other hand, have a large side-effect profile including gastrointestinal bleeding, renal toxicity, and cardiovascular concerns which limits their use in cancer pain management. Nevertheless, NSAIDs appear to be especially useful for the treatment of pain due to bone metastases and inflammatory pain. It is advised to use any NSAIDS that the patient has found effective and well-tolerated; otherwise ibuprofen may be used for daily maximum dose of 3,200 mg.

**WEAK OPIOIDS**

The WHO ladder approach distinguishes weak opioids and strong opioids for cancer pain management. Weak opioids are commonly used in combination with non-opioid agents for managing moderate cancer pain and for patients who have limited exposure to opioids. Potency of these drugs is limited by their characteristics or the limitations of the maximal dosage of the product it is combined with. This group of drugs includes hydrocodone, tramadol and codeine. Codeine is not commonly used nowadays due to its large side effect profile and weak efficacy.

Non-opioid combinations with oxycodone may be considered weak opioids because
the non-opioid component limits the dosing of these products. The doses of these weak opioids can only be escalated until non-opioid components each their maximum allowed doses. Since the maximum amount of acetaminophen per dosage unit in the combination products is reduced to 325 mg, the total daily amount of hydrocodone or oxycodone increased, which is still appropriate for managing moderate pain. Tramadol, due to its mechanism that is partly opioid and partly norepinephrine and serotonin reuptake inhibition, presents a unique advantage in that it may also benefit cancer patients that are experiencing mild to moderate neuropathic pain.

STRONG OPIOIDS

Strong opioids are typically pure mu receptor agonists which can be used in opioid tolerant patients or in patients with moderate to severe pain. The most commonly used strong opioids include morphine, oxycodone, hydromorphone, oxymorphone, fentanyl, and methadone. Most of the potent opioids have a duration of action around three to four hours, requiring frequent oral dosing of immediate-release formulations. They are useful for initial dose titrations but not optimal for managing persistent cancer pain. Long-acting or modified-release formulations of oral opioids are thus more desirable. Methadone is long-acting and available in immediate oral solution and tablets.

Strong opioids can also be administered by injection; however, they are typically inappropriate for chronic pain management. Rectal suppositories are also available commercially for morphine and hydromorphone when upper GI tract cannot be used and the parenteral route is not available. Societal taboos may be a barrier to acceptance of the rectal route; adequate education and counseling may lower or eliminate this barrier. It is important to educate patients and caregivers that rectal administration is typically not a first line therapy and reserved for situations in which the oral and or parenteral route are not feasible. An example would be a patient being managed at home with severe nausea without a parenteral access for administration of injectable medication. The rectal administration of opioids may not be the best option in cancer patients who are at risk for bleeding or infection as suppository bases may irritate or dehydrate the rectal tissue.

Morphine is widely used because of extensive research, clinical experience and availability in a variety of oral and parenteral formulations. Available oral modified-release products include MS Contin®, Oramorph®, Avinza®, and Kadian®. Avinza and Kadian are capsules containing extended-release morphine beads which can be sprinkled on apple sauce if patients cannot swallow whole tablets. Kadian beads may also be used for administration through a 16 French gastrostomy tube. Due to its potentially toxic metabolite, morphine-3-glucuronide, morphine may not be the best option for patients with renal insufficiency or those requiring chronic administration of large doses.

Hydromorphone has better oral bioavailability, is more soluble, and more potent than morphine. Its overall pharmacologic profile parallels that of morphine. The extended-release tablet Exalgo® utilizes an osmotic release which is designed to release drug at a controlled rate and provides continuous, around-the-clock analgesia. Hydromorphone is also metabolized to the potentially toxic hydromorphone-3-glucuronide metabolite. The use of hydromorphone should be cautioned in patients with renal insufficiency or those requiring chronic large doses.

Oxymorphone is more potent than morphine, but it has a lower oral bioavailability (approximately 10 percent). Opana®, the oral formulation of oxymorphone, is available in both immediate release and extended-release preparations. A theoretical advantage to oxymorphone is that it is associated with little to no pharmacokinetic drug interactions. It is important to note that oxymorphone has the same pharmacodynamic drug interactions as all other strong opioids. Oxymorphone is currently only available in a brand name product and can be very costly for patients without insurance.

Oxycodone is approximately 1.5 to 2 times as potent as morphine. Oxycodone is available orally as an immediate release tablet, capsule, liquid, and as an extended release product (OxyContin®). There is no parenteral formulation of oxycodone available in the United States. Whereas morphine and hydromorphone go through
phase two metabolism, oxycodone primarily goes through phase one metabolism and thus a better option for cancer pain patients with renal insufficiency.

Methadone remains an option for managing cancer pain because of its unique mechanism of action and low cost. Besides working at the mu receptor, methadone also weakly inhibits the reuptake of serotonin and noradrenaline and weakly inhibits the n-methyl-D-aspartate receptor. These additional properties make methadone an attractive option for cancer patients experiencing moderate to severe neuropathic and nociceptive cancer pain. Another advantage to methadone is its quick onset of action and longer duration of action. Once steady state has been reached, it can typically be dosed every eight to 12 hours. Though methadone is longer acting, it has a highly variable half-life and is widely distributed in the tissues. Moreover, the analgesic relief profile does not match the pharmacokinetic profile which makes dosing of methadone challenging. Methadone should only be used in patients when their pain is not well-managed by other opioids. Methadone should be started at low doses and titrated slowly. Selecting an appropriate starting dose of methadone represents a major challenge for clinicians since there are many ranges available. Starting doses will depend upon the type of pain, severity, route of administration, reference range utilized among other factors. A safe initial daily dose range of methadone for many patients is between 7.5–10 mg per day. Converting methadone from another opioid represents another major challenge as many different conversion factors are available, each often giving a different methadone dose. When converting to methadone from another opioid, the initial doses can often be higher than 7.5–10 mg per day. Patients on methadone should be monitored closely to watch for signs of drowsiness and respiratory depression. For patients who are on high doses of methadone or patients at risk of arrhythmia, ECG monitoring for QT interval prolongation may become necessary. Another disadvantage of methadone is it can be associated with many drug interactions as it is metabolized by several of the cytochrome P450 (CYP) enzymes. It is highly recommended that methadone be utilized by clinicians familiar with its unique properties.

Fentanyl is a highly lipophilic opioid and is approximately 100 times more potent than morphine. Fentanyl undergoes extensive first-pass metabolism, and is primarily metabolized by CYP 3A4. Transdermal fentanyl (Duragesic®) is a very useful product for stabilized chronic pain management therapy since it provides controlled drug release for 72 hours. Absorption of fentanyl through skin is slow and minimum effective concentration is seen around 12 hours. Peak serum concentrations of fentanyl generally occurred between 30 and 72 hours after initial application and steady state concentration is achieved with the second patch. After removal of the patch, fentanyl is continuously absorbed from the skin depot where fentanyl accumulated during the application of the patches. It takes approximately 20–27 hours for 50 percent serum concentration to decline, therefore caution should be taken when converting from transdermal fentanyl to another long-acting opioid preparation. Patient variability should be specially considered because that can affect fentanyl absorption. An elevated body temperature of 40°C (104°F) may increase fentanyl absorption by about one third. Additionally, cachectic patients who have low body weight may have altered pharmacokinetics which makes fentanyl dosing difficult. It is also very important to properly dispose of ALL fentanyl products. Inappropriate disposal of fentanyl products can result in very serious and even fatal consequences for children and pets.

Pharmacists in the outpatient and mail-order pharmacy setting are required to provide patients with the product-specific Medication Guide when dispensing extended-release long-acting opioid products mentioned previously. Patients should be advised to not break, chew, crush, dissolve or inject these medicines. Alcohol should be avoided while taking these products as alcohol may accelerate the drug release from these extended-release products and cause dose dumping effect, potentially resulting in overdose or even death. These opioid products should be stored away from children and in a safe place. Unused medicine should be flushed down the toilet.

**MIXED OPIOID AGONIST-ANTAGONIST**

Mixed opioid agonist-antagonists were developed to try to minimize several of the major
concerns associated with pure opioids including: respiratory depression and misuse, abuse, and addiction. Many medications exist within this class, though the classic example is pentazocine. Medications within this class have a couple of disadvantages that do not make them practical for use in cancer pain management. First, these medications have a maximal effect (ceiling effect) because of their pharmacological properties. These medications are also associated with many side effects, particularly psychotomimetic effects. One mixed opioid agonist-antagonist that can be considered for management of chronic cancer pain is buprenorphine. Buprenorphine is a partial mu agonist and a kappa antagonist. Due to its binding properties it does not appear to cause as many psychotomimetic effects as typical opioid agonist-antagonists. Buprenorphine also comes in a transdermal formulation, and a conversion from oral morphine is provided in Table 5. If buprenorphine is going to be used in cancer pain management it is very important to monitor the patient’s response to breakthrough medication as there is a chance the buprenorphine could lessen the effects of a pure opioid agonist breakthrough medication.

**SELECTION OF AN APPROPRIATE OPIOID**

The selection of an appropriate opioid for managing cancer pain depends on many factors including previous patient responses, adverse effects, patient status, practitioners’ preferences, degree of opioid tolerance, and cost. Consideration for conversion factors are vital when switching a patient from one opioid to another to avoid sub-therapeutic treatment causing inadequate pain relief, or supratherapeutic treatment causing increased adverse drug effects. Equivalent dose for the new opioid can be estimated using a conversion chart (see Table 1) comparing potency and equivalences to morphine. Conversions are needed anytime you are switching between dosage forms of the same opioid or when you are changing to a different opioid. When changing to a different opioid, it is often necessary to reduce the equivalent dosage by 30–50 percent to account for inter-patient variability and the lack of cross-tolerance between opioids. Cross-tolerance reduction is not required when you are changing the dosage form of the same opioid or if the patient’s pain is currently severely undertreated. Methadone has a variable oral conversion ratio (Table 3) and should be prescribed only by a practitioner or specialist familiar with its use. An example of an opioid conversion is provided in the case of PS, a 48-year-old female with chronic back pain due to a motor vehicle accident. Her pain is well controlled (she rates it a 2/10), she is on oxycodone ER 20 mg bid, and oxycodone iR 5 mg tablets q four hours as needed—takes an average of three per day. Her insurance will not pay for brand name oxycodone ER, and the doctor would like to change her over to long-acting morphine. Please provide the doctor with the most appropriate dose of morphine ER, and morphine IR breakthrough dose.

**Step 1:** Identify both the current and desired drug, dose, route, and dosing interval

**Current:** Oxycodone ER 20 mg bid and an average of three tablets of 5 mg oxycodone every four hours as needed
Moreover, the duration of action of oral immediate-release opioids last usually around three to four hours, which leads to overtreatment of the breakthrough pain. Parenteral opioids offer an ideal onset of action, though their duration of action is still three to four hours. Additionally, parenteral opioids do not possess an easy or convenient route of administration for patients at home. To improve the quality of life for cancer patients, a variety of innovative transmucosal immediate-release fentanyl (TIRF) products have appeared on the market recently. Oral transmucosal products include Actiq, Fentora, Onsolis, Abstral, and Subsys. Lazanda is an intranasal transmucosal product.

Actiq®, (oral transmucosal Fentanyl citrate, otFc), was the first transmucosal product approved by the FDA to treat breakthrough pain. It is a lozenge made of a dissolvable sugar-based matrix on a plastic handle. It is designed to be self-administered. Patients should not chew the lozenge, as chewing and swallowing the lozenge negates the benefits of transmucosal delivery. Instruct the patient to actively move the lozenge up and down their cheek and between cheeks with a goal to consume the lozenge within 15 minutes. Patients with dry mouth may need to moisten their mouth prior to use. Actiq is available in six dosage strengths: 200, 400, 600, 800, 1,200 or 1,600 mg of fentanyl citrate. Approximately 25 percent of the drug is absorbed through the buccal mucosa to produce a rapid onset of analgesic effect, with the remaining 75 percent of the drug swallowed and then slowly absorbed in the GI tract. The average time to onset of effect is about 5–10 minutes. The median time of maximum plasma concentration (Tmax) for different doses of OTFC varies from 20–40 minutes (range of 20–480 minutes). The absolute bioavailability of Actiq is about 50 percent compared to intravenous fentanyl. If an episode of breakthrough pain is not relieved 15 minutes after finishing the lozenge (30 minutes after start), the patient may repeat with one additional lozenge. Once pain relief is achieved, the lozenge should be

**TREATMENT OPTIONS FOR BREAKTHROUGH CANCER PAIN**

It has been reported that more than 80 percent of cancer patients who have chronic persistent pain also experience breakthrough pain. Breakthrough pain is a transitory exacerbation of moderate to severe pain, which reaches peak intensity within a few minutes with a duration of 30 minutes to an hour. There are three subtypes of breakthrough pain, including incident pain, spontaneous pain and end of dose failure.

Breakthrough pain should be managed with a rapidly acting opioid with a short duration of action. Traditionally breakthrough pain is managed by oral immediate-release opioids, such as oral morphine solutions. However, these agents often fail to provide fast and adequate pain relief because of the slow gastrointestinal absorption of opioids. Patients usually have to suffer at least 30 minutes of moderate to severe breakthrough pain before the onset of orally administered opioids.

**Step 2**: Determine amount of current total daily drug dose (TDD) in 24 hours

Oxycodone ER 20 mg x 2 = 40 mg
Oxycodone 5 mg x 3 = 15 mg
Total 24-hour oxycodone = 55 mg

**Step 3**: Reduce 24-hour dose by 1/3 when the patient’s pain is well controlled when changing from one drug to another to account for inter-patient variability and incomplete cross tolerance

55 mg x 0.67 = 36.85 mg oxycodone

**Step 4**: Set up a ratio to determine amount of desired drug/24 hr. Use Equianalgesic Chart

\[
\text{TDD current opioid} \times \frac{\text{equianalgesic factor of new opioid}}{\text{equianalgesic factor of current opioid}} = \text{TDD new opioid}
\]

\[
36.85 \text{ mg oxycodone} \times \frac{55 \text{ mg (from chart)}}{30 \text{ mg (from chart)}} = 55 \text{ mg of daily oral morphine}
\]

**Step 5**: Select appropriate dosing interval

55 mg morphine in 24 hours.
30 mg morphine ER twice daily
Do not forget to add a breakthrough regimen for these patients.
removed from the mouth and properly disposed. Actiq is dosed no more frequently than every four hours to reduce the risk of overdose. Pharmacists should help ensure that the patient has only one strength in their home to avoid confusion or overdose.

Fentora® is a buccal effervescent tablet designed to be placed and retained between the upper gum and check above a molar for a period sufficient to allow disintegration of the tablet and absorption of fentanyl across the oral mucosa. It is believed that when Fentora comes in contact with saliva, an effervescent reaction takes place resulting in a transient decrease in pH to facilitate drug dissolution. After the liberation of carbon dioxide, the pH of the tablet microenvironment rises to enhance the permeation of fentanyl through the oral mucosa. Fentora is available in five dosage strengths: 100 mcg, 200 mcg, 400 mcg, 600 mcg and 800 mcg. Clinical trials demonstrated faster drug absorption and greater bioavailability (around 65 percent) from Fentora compared to Actiq. Approximately 50 percent of the total dose administered is absorbed transmucosally, and the remaining half of the dose is swallowed and undergoes more prolonged absorption from the GI tract. Important counseling points for Fentora include ensuring a moist mouth prior to tablet use for those patients with dry mouth, using the opposite side of the mouth if more than one tablet is required for the pain episode, and allowing the tablet to dissolve without the aid of sucking, chewing, or additional water. However, additional water can be used after 30 minutes to aid in swallowing any remaining portions of the tablet. If an episode of breakthrough pain is not relieved 30 minutes after placing the tablet, the patient may repeat once. Fentora is dosed no more frequently than every four hours to reduce the risk of overdose.

Onsolis® is a buccal fentanyl soluble film with a bio-adhesive side in which drug is dispersed and an inactive backing layer which minimizes the amount of fentanyl that is swallowed. Onsolis is designed to adhere to the buccal mucosa within five seconds and the whole film should completely dissolve within 15 to 30 minutes. This product is designed to reduce continuous patient participation in dosing, which may provide a more reliable analgesic effect. Onsolis is available in five dosage strengths: 200 mcg, 400 mcg, 600 mcg, 800 mcg, and 1,200 mcg. Onsolis doses must be titrated beginning with a 200 mcg dose; it is not appropriate to predict a dose based on

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### Table 2: Fentanyl Transdermal Dosing: Per Duragesic® Package Insert

<table>
<thead>
<tr>
<th>Oral 24-hour Morphine Dose (mg/day)</th>
<th>DURAGESIC® (mcg/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60–134</td>
<td>25</td>
</tr>
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<td>135–224</td>
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<td>275</td>
</tr>
<tr>
<td>1,035–1,124</td>
<td>300</td>
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</tbody>
</table>

Notes regarding fentanyl transdermal conversion:
- Wide ranges of oral morphine equivalents (OME) exist for each patch strength.
- Chart is established to convert from OME to fentanyl transdermal, not from fentanyl transdermal to OME—risks overdose of the new agent.
- This conversion chart is conservative. It may be too low for some patients, which is an additional reason to monitor your patients very closely during opioid conversions.
A larger absorption surface area than the buccal area and is highly vascularized. In addition, absorption through olfactory mucosa may offer a rapid, direct route to deliver drug to the brain. Therefore it is expected to observe faster onset of action and greater bioavailability from intranasal absorption. A clinical study compared the relative bioavailability of Lazanda with an oral transmucosal fentanyl citrate product, and the bioavailability of fentanyl from Lazanda was approximately 20 percent higher. Like other TIRF products, it is not appropriate to predict a dose based on daily maintenance doses. Patients must start with a 100 mcg and titrate up to the effective and tolerable dose. If the dose requires more than one spray (such as a 200 mcg during titration) the patient should use one spray in each nostril. If an episode of breakthrough pain is not relieved after 30 minutes, the patient may repeat once with a dose of the same strength. Lazanda is dosed no more frequently than every two hours to reduce the risk of overdose.

Patients on oral maintenance opioid therapy who require a change to an intranasal fentanyl product should follow the same conservative approach. Conversion to a larger absorption surface area than the buccal area and is highly vascularized. In addition, absorption through olfactory mucosa may offer a rapid, direct route to deliver drug to the brain. Therefore it is expected to observe faster onset of action and greater bioavailability from intranasal absorption. A clinical study compared the relative bioavailability of Lazanda with an oral transmucosal fentanyl citrate product, and the bioavailability of fentanyl from Lazanda was approximately 20 percent higher. Like other TIRF products, it is not appropriate to predict a dose based on daily maintenance doses. Patients must start with a 100 mcg and titrate up to the effective and tolerable dose. If the dose requires more than one spray (such as a 200 mcg during titration) the patient should use one spray in each nostril. If an episode of breakthrough pain is not relieved after 30 minutes, the patient may repeat once with a dose of the same strength. Lazanda is dosed no more frequently than every two hours to reduce the risk of overdose.

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Table 3: Conservative Approach to Convert to Transdermal Fentanyl from OMEs or From Transdermal Fentanyl to OMEs

<table>
<thead>
<tr>
<th>OMEs per Day</th>
<th>Transdermal Fentanyl (mcg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg</td>
<td>12.5</td>
</tr>
<tr>
<td>50 mg</td>
<td>25</td>
</tr>
<tr>
<td>100 mg</td>
<td>50</td>
</tr>
<tr>
<td>150 mg</td>
<td>75</td>
</tr>
<tr>
<td>200 mg</td>
<td>100</td>
</tr>
</tbody>
</table>
due to a large surface area and high vascular-
ization of the lungs, which potentially can reduce
the onset of action of fentanyl to be less than
one minute. Several inhalation products are still
under clinical trials and only time will tell if these
products will make it to market as clinically
meaningful products. Mixed at best results have
been seen when fentanyl has been delivered
via the pulmonary route for dyspnea in palliative
care and hospice patients.

Initially the FDA approved individual Risk
Evaluation and Mitigation Strategy (REMS)
for some of these TIRF medicines. To reduce
the burden on prescribers and pharmacists, a
single shared REMS program was approved
by the FDA, which began in March 2012. The
REMS program aims to reduce the risk of
misuse, abuse, addiction, and overdose with
these TIRF medicines (www.tirfremaccess.
com). Health care providers that prescribe TIRF
medicines for out-patient use are required to
enroll in the TIRF REMS Access program. Both inpatient
and outpatient pharmacies are required to enroll in this
TIRF REMS Access program to dispense TIRF medicines.
Prescribers and pharmacies will be required to re-enroll
in the TIRF REMS program every two years from the date
of enrollment into the TIRF class REMS or into the indi-
vidual REMS, whichever was earlier. A designated autho-
rized pharmacist must complete enrollment on behalf of
the pharmacy, which requires reviewing the education
program, successfully completing the knowledge assess-
ment, and complete an enrollment form. The authorized
pharmacist will then train other pharmacy staff in the ap-
propriate dispensing of TIRF medicines, according to the
TIRF REMS Access program.

Appropriate patient selection is one of the key safety
requirements. These TIRF medicines are indicated only
for the management of breakthrough pain in adult cancer
patients 18 years and older who are already receiving
and who are tolerant to around-the-clock opioid therapy
for their underlying persistent cancer pain. The only
exception is for Actiq brand and its generic equivalents,

<table>
<thead>
<tr>
<th>Evidence Source</th>
<th>OME : Oral Methadone Ratio</th>
<th>Mercadente</th>
</tr>
</thead>
<tbody>
<tr>
<td>OME 30–90 mg mg</td>
<td>4 : 1</td>
<td>4 : 1</td>
</tr>
<tr>
<td>OME 90–300 mg</td>
<td>6 : 1</td>
<td>8 : 1</td>
</tr>
<tr>
<td>OME &gt;300 mg</td>
<td>8 : 1</td>
<td>12 : 1</td>
</tr>
</tbody>
</table>

Notes regarding oral methadone conversions:
• Many methods exist to convert from OME to methadone and only some are listed above.
• Methadone conversions to and from OMEs are not linear and this can complicate conversion.
• Because of the differences in the published conversion factors to and from methadone, it is best to consult an experienced clinician
prior to changing a patient to or from methadone.

### Table 4: Methadone Oral Conversions

<table>
<thead>
<tr>
<th>Total Daily Baseline OME</th>
<th>Estimated Daily Oral Methadone Requirement as% of total daily OME</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;100 mg</td>
<td>20–30%</td>
</tr>
<tr>
<td>100–300 mg</td>
<td>10–20%</td>
</tr>
<tr>
<td>300–600 mg</td>
<td>8–21%</td>
</tr>
<tr>
<td>600–900 mg</td>
<td>5–10%</td>
</tr>
<tr>
<td>&gt;1,000 mg</td>
<td>&lt; 5%</td>
</tr>
</tbody>
</table>
which are indicated for cancer patients 16 and older. TIRF medicines are contraindicated in opioid naive patients, or in the management of acute postoperative pain. Life-threatening respiratory depression could occur at any dose in these patients.

The products indicated for the management of breakthrough pain are not bioequivalent on a microgram-per-microgram basis. The differences in the pharmacokinetics of these products relative to each other could potentially result in clinically significant differences in the amount of fentanyl absorbed and could result in serious adverse events such as a fatal overdose. Substitutions are only allowed between Actiq and its generic equivalents. Directions for safely converting patients from one product to another product are currently unavailable except for converting patients from Actiq to Fentora. In all other cases, it is necessary to individually titrate each patient’s dose to provide adequate analgesia while minimizing side effects. Patients beginning treatment with a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if they have taken another TIRF medicine. The use of TIRF medicines should be limited to four or fewer doses per day. Otherwise, increasing the around-the-clock opioid medicine should be considered.

### MANAGING OPIOID SIDE EFFECTS

Opioid related adverse effects are common, but they do tend to improve over time with the exception of constipation. Constipation, nausea, vomiting, pruritus, sedation, and delirium are all common side effects of opioids. It is important to manage these side effects appropriately and aggressively. Though respiratory depression is uncommon, it is a very serious adverse effect of opioids and respirations should be monitored closely.

Constipation is the one common side effect of opioids that does not generally improve over time, as patients will not develop tolerance to constipation. Opioids primarily cause constipation by decreasing the propulsive activity of the intestine and increasing absorption of fluid and electrolytes from the intestine. Measures should be taken to prevent constipation, such as treating prophylactically and encouraging adequate fluid and dietary fiber intake for the patient. The use of fiber supplements is cautioned in patients who have low mobility or are bed-ridden, as stool-bulkening can often worsen the scenario. Prophylactic and acute treatment medications include the osmotic polyethylene glycol or stimulant laxatives, senna, and bisacodyl with or without a stool softener. Generally, a stool softener alone is not sufficient therapy as stool softeners do not help to reverse the slowing of the intestine caused by opioids. If constipation is unresponsive to standard treatments, consider adding another agent such as a suppository, enema, osmotic laxative (such as magnesium citrate, lactulose, or polyethylene glycol), or a prokinetic agent (such as metoclopramide). Relistor® (Methylnaltrexone Injection), is a prescription-only medication approved for opioid induced constipation in palliative care patients. Methylnaltrexone is a peripheral mu receptor antagonist and works by blocking the action of opioids on intestinal mu receptors. This medication is given by the subcutaneous route and is typically reserved for constipation resistant to other treatment modalities.

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**Table 5: Buprenorphine Transdermal Patch (Butrans®)**

<table>
<thead>
<tr>
<th>Oral morphine equivalents (OMEs)</th>
<th>Patch strength</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30 mg OME</td>
<td>5 mcg</td>
</tr>
<tr>
<td>30–80 mg OME</td>
<td>10 mcg</td>
</tr>
<tr>
<td>&gt; 80 mg OME</td>
<td>20 mcg</td>
</tr>
</tbody>
</table>

Notes regarding buprenorphine transdermal patch:
- Do not exceed 20 µg dose because of risk of QTc prolongation.
- Is applied once weekly to manage chronic moderate to severe pain.
- Use caution applying to a patient requiring large opioid doses.
- Monitor pain response to breakthrough pain medications.
Nausea caused by opioids is common and related to several mechanisms. Understanding the mechanisms associated with nausea and vomiting can allow more targeted pharmacotherapy versus empiric treatment. One mechanism through which opioids cause nausea is stimulation of the D2 receptor in the chemoreceptor trigger zone. Another possible mechanism is a result of gastric stasis and constipation. Prophylactic treatment for nausea using antiemetic medication is recommended if the patient has a history of opioid induced nausea. It is important to remember that if a cancer patient is simultaneously receiving chemotherapy along with opioids, the chemotherapy could also be contributing to the nausea and vomiting. Chemotherapy typically induces nausea and vomiting by stimulation of the 5HT3 receptors in the chemoreceptor trigger zone and the gut wall. It is also important to consider route of administration, severity of nausea, duration of nausea, comorbid conditions, and cost when developing a treatment plan for nausea in a cancer patient taking opioids. There are many antiemetic agents to consider including metoclopramide, prochlorperazine, promethazine, haloperidol, ondansetron (and other 5HT3 receptor antagonists), and meclizine. Metoclopramide is a logical first-line treatment consideration for nausea caused by opioids as metoclopramide is a D2 receptor antagonist and promotes gastric motility. Other D2 receptor antagonists include prochlorperazine, promethazine, and haloperidol. Prochlorperazine offers a practical advantage of being available as a suppository in addition to a tablet. Promethazine can be compounded into a gel, but its use is cautioned as this medication is very sedating and can worsen the sedation caused by opioids. Haloperidol can be effective, although it is typically reserved for palliative care and hospice patients. 5HT3 receptor antagonists should be considered as a first-line option in addition to a dopamine blocking agent in a cancer patient receiving both opioids for pain management and chemotherapy for the treatment of the cancer. Muscarinic and histamine antagonists such as meclizine are not routinely utilized for opioid related nausea as monotherapy, although it can be added on for more resistant cases.

Pruritus caused by opioids is believed to be primarily related to mast cell destabilization and is seen more often with the natural occurring or semi-synthetic opioids. More recent data suggests that a portion of pruritus could be related to a central serotonin mechanism. Management of pruritus can be tried using oral antihistamines such as diphenhydramine or hydroxyzine. Monitor the patient closely if antihistamines are utilized as they can increase sedation caused by opioids. Topical products can also be utilized for opioid induced pruritus, although utility of topical products might be limited if the pruritus covers a large area. If the pruritus is persistent and cannot be oppressed, consider rotating to a different analgesic agent. Though not routinely recommended, including small doses of nalbuphine or naloxone to stop the pruritus while maintaining adequate analgesia can be tried.

Opioid sedation can greatly decrease a patient’s quality of life, and often is a reason why patients will discontinue it. Thus, management of opioid-induced sedation is very important to maximize a cancer patient’s quality of life, especially since the cancer itself can also cause fatigue and sedation. Minimizing opioid induced sedation may be accomplished by using the lowest tolerable analgesic dose. Monitoring the patient is vital with this option as they may experience withdrawal or subtherapeutic pain management. Another option is to add another drug that will counteract the sedating effects, such as dextroamphetamine, methylphenidate, or modafinil. The use of central nervous system stimulants to counteract opioid drowsiness is considered an off-label indication for these medications. CNS stimulants should only be used for a short period of time, as a last resort, and should not be used at night time to avoid insomnia. If sedation persists, opioid rotation may help in decreasing sedation. It is also important to review the patient’s medication profile and try to avoid use of other sedating medications.

Respiratory depression is a serious but uncommon adverse effect of opioids. Naloxone is the drug of choice for reversal of respiratory depression. Administration of naloxone should be done carefully and typically no more often than every 30–60 seconds. It may be prudent to start with doses as low as 0.1 mg, monitor closely and repeat
doses of 0.1 mg until the patient responds. This dosing strategy is aimed at reversing the respiratory depression but not analgesia. Along with reversing respiratory depression, large doses can reverse analgesia, cause withdrawal, or cause a pain crisis. Response should take place within 10 minutes or a total naloxone dose of 1mg. Care should also be taken when patients are using long-acting products such as methadone or transdermal fentanyl, as they may require subsequent doses.

Delirium in a cancer patient requires careful assessment as it could have many causes. Delirium could be caused by disease progression, electrolyte imbalances, medications, or pain itself. If the delirium is believed to be caused by the opioid, consider changing to a different opioid or consider adding a non-opioid analgesic to the current regimen and reducing the opioid dose. Adding an opioid sparing agent may allow for appropriate pain management while reducing the opioid induced delirium. If decreasing the opioid dose is not an option and treatment for the delirium is required, consider the addition of a neuroleptic medication such as haloperidol, olanzapine, or risperidone to control delirium episodes.

MANAGEMENT OF NEUROPATHIC CANCER PAIN
Neuropathic pain results from damage or dysfunction of the somatosensory nervous system and is a common condition that can occur in cancer patients. Cancer can cause neuropathic pain via nerve compression, injury by primary or metastatic tumors, or by cancer treatments. Both chemotherapy agents and radiation used in the treatment of cancer can cause neuropathies. Vinca Alkaloids, platinum compounds, and taxanes are common drugs that cause neuropathies. Neuropathies induced by chemotherapy agents are usually, but not always, reversible on discontinuation or reduction in dose, but the reversal can take from months to years. Treatment of cancer neuropathic pain is important as untreated pain decreases the patient quality of life, can delay cancer treatment, result in chemotherapy dose reductions, or even discontinuation of therapy. Thus it is very important for a pharmacist to be able to recognize patients who are at risk for developing neuropathic pain from cancer as well as ensuring the patient is receiving both appropriate treatment and medication counseling. Identifying cancer patients at highest risk for developing neuropathic pain is an important first step. A list of common chemotherapeutic agents associated with cancer neuropathic pain is provided in Table 6.

Recognizing common symptoms of neuropathic pain is critical, and a pharmacist should be able to distinguish these symptoms from nociceptive pain. Nociceptive pain is commonly described as dull, achy, pressure-like pain, whereas neuropathic pain is usually described as burning, stinging, needle-like, stabbing, jolting, or knife-like pain. Spontaneous or evoked unpleasant abnormal sensations (dysesthesia), non-painful spontaneous abnormal sensations (paresthesia), and pain arising from a non-painful stimulus (alldynia) are also signs of neuropathic pain. In addition to painful symptoms, visible skin changes and loss of sensation are observable in some patients.

<table>
<thead>
<tr>
<th>Table 6: Chemotherapeutic Agents Known to Cause Peripheral Neuropathy</th>
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<tbody>
<tr>
<td><strong>Sensory symptoms</strong></td>
</tr>
<tr>
<td>Bortezomib</td>
</tr>
<tr>
<td>Carboplatin</td>
</tr>
<tr>
<td>Cisplatin</td>
</tr>
<tr>
<td>Gemcitabine</td>
</tr>
<tr>
<td>Misonidazole</td>
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<tr>
<td>Oxaliplatin</td>
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<tr>
<td>Procarbazine</td>
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<tr>
<td>Thalidomide</td>
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www.americaspharmacist.net
After a cancer patient has been identified as experiencing neuropathic pain, the next step is to ensure the patient is receiving appropriate pharmacotherapy. Selecting the best medication for neuropathic pain proves challenging as no magic bullet exists, particularly for cancer neuropathic pain. Pharmacotherapy for painful peripheral neuropathies, such as cancer neuropathic pain, is one of the most flawed as no clear consensus guidelines exist and clinicians often prescribe incorrect drugs. Ineffective drugs such as NSAIDs are still used in general practice to treat neuropathic pain, and inappropriate doses of recommended drugs are often used. Pharmacists, therefore, have a pivotal role in advising patients as well as other health care providers on the appropriate usage of medications, with the products currently available to manage neuropathic pain. Understanding the neurobiology and pathophysiology of cancer neuropathic pain, and knowledge of current therapies available are crucial for the development of effective individual pain management strategies.

Historically, neuropathic pain was treated mainly using tricyclic antidepressants and first generation anticonvulsants because the traditional non-opioid analgesics provided inconsistent pain relief in most patients. Opioids have been found to be useful in treating neuropathic pain in many patients. However due to controversies in clinical trial outcomes and due to the high incidence of adverse effects plus high addiction potential, use of opioids is limited in treating neuropathic pain. Fortunately, clinical observations and advances in the knowledge of pain neurobiology have recently led to improvements in the pharmacotherapeutic management of neuropathic pain. Current treatment options for neuropathic pain include antidepressants, anticonvulsants, opioids, topical analgesics, and combination therapies. Though many options are available, not one specific agent or class of agents has been shown to be superior in the management of cancer neuropathic pain.

Several factors go into consideration when individualizing neuropathic pain management strategies for cancer patients. These factors include efficacy and tolerability of medication, comorbid conditions that may benefit or worsen from therapy, potential for medication interactions, and cost of therapy. It is important to remember that the management of cancer neuropathic pain is complicated and often coexists with other types of pain. As previously discussed, in addition to neuropathic pain, cancer patients can experience visceral, somatic, and bone pain. Management of patients experiencing coexisting pain types presents a challenge as multiple different medications are often required. Efficacy of pharmacotherapy utilized in neuropathic pain is an important consideration when individualizing therapy. Very little data exists specifically related to management of cancer neuropathic pain. In fact, most data regarding management of neuropathic pain is related to diabetes mellitus or post-herpetic neuropathy. Data suggest medication efficacy is unpredictable, and those agents routinely effective in the management of diabetes and post-herpetic neuropathy may not always be effective in cancer neuropathic pain. Medication tolerability is an important consideration as the patient’s underlying cancer symptoms may augment medication side effects. Examples of these side effects include nausea, vomiting, and somnolence. Additionally, medications used in the treatment of neuropathic pain are associated with complicated dosing regimens and a delayed onset of action.

Knowing the facts discussed above is important as the selection of the best medication or medication combination often requires a stepwise process. This stepwise process is often time consuming, contributing to the difficulties and frustrations that come with treating cancer patients with neuropathic pain. A brief review of common medication classes used in the management of neuropathic pain is provided below. It is important to remember that most data regarding these medication classes is extrapolated from studies related to diabetic and post-herpetic neuropathic pain. A summary table of commonly used antidepressant and anticonvulsant medications used in neuropathic pain has also been provided.

**Antidepressants**

Antidepressants, especially tricyclic antidepressants (TCAs), have historically been the mainstay of treating neuropathic pain. Several factors go into consideration when individualizing neuropathic pain management strategies for cancer patients. These factors include efficacy and tolerability of medication, comorbid conditions that may benefit or worsen from therapy, potential for medication interactions, and cost of therapy. It is important to remember that the management of cancer neuropathic pain is complicated and often coexists with other types of pain. As previously discussed, in addition to neuropathic pain, cancer patients can experience visceral, somatic, and bone pain. Management of patients experiencing coexisting pain types presents a challenge as multiple different medications are often required. Efficacy of pharmacotherapy utilized in neuropathic pain is an important consideration when individualizing therapy. Very little data exists specifically related to management of cancer neuropathic pain. In fact, most data regarding management of neuropathic pain is related to diabetes mellitus or post-herpetic neuropathy. Data suggest medication efficacy is unpredictable, and those agents routinely effective in the management of diabetes and post-herpetic neuropathy may not always be effective in cancer neuropathic pain. Medication tolerability is an important consideration as the patient’s underlying cancer symptoms may augment medication side effects. Examples of these side effects include nausea, vomiting, and somnolence. Additionally, medications used in the treatment of neuropathic pain are associated with complicated dosing regimens and a delayed onset of action.

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neuropathic pain. Tricyclic antidepressants are considered first-line agents for many neuropathies, though efficacy in cancer neuropathic pain has not been proven. It is widely accepted that oral TCAs have an analgesic effect in neuropathic pain. The analgesic mechanism of TCAs is believed to be the non-selective inhibition of monoamine reuptake in the neuronal junctions of the CNS. Norepinephrine (NE) and serotonin (5-HT) are the major neurotransmitters in the descending inhibitory system that extends from the supraspinal brain center to the spinal cord. This inhibition increases the levels of these monoamines and might increase the pain inhibition in the CNS. It should be remembered that the mean dose required for pain reduction with antidepressants are usually lower than doses necessary to treat depression. For neuropathic pain, it is suggested to start with 10–25 mg at bedtime and increase slowly by 10–25 mg increments to 100–150 mg at bedtime. Amitriptyline, imipramine, desipramine, and nortriptyline are the most commonly used TCAs. Unfortunately, the analgesic effect of the TCAs is tempered by their side effect profiles, with somnolence and dry mouth being the predominant side effects. Side effects can be minimized by giving them at bedtime, slow titration, and use of the TCAs with secondary amine structure, nortriptyline and desipramine, as they are associated with less anticholinergic side effects than the tertiary amines. Any TCA should be cautioned in a geriatric patient because of their anticholinergic side effects, which increase risk of confusion and falls. A potential benefit of TCAs is their ability to help treat depression or insomnia, conditions that can also be seen in cancer patients. Two other practical benefits are their once daily dosing and inexpensive cost.

Selective serotonin and norepinephrine reuptake inhibitors (SNRIs) are used to treat a variety of neuropathic pains, though specifically related to cancer neuropathic pain is very limited. Both duloxetine and venlafaxine share a mechanism of action similar to TCAs but have the advantage of fewer anticholinergic side effects. Each of these medications should be started at a low dose and slowly titrated to minimize side effects. Utilization of SNRIs in cancer neuropathic pain patients with comorbid depression may also result in an improvement of both pain and depression. The SNRIs can be considered as a first line treatment option in many cancer neuropathic pain patients. Use of venlafaxine is limited by its potential to increase blood pressure and small potential to cause cardiac conduction abnormalities. One limitation to the use of duloxetine could be its relatively high cost, especially to those patients without insurance. Use of milnacipran is currently not recommended for cancer neuropathic pain as it has been primarily studied only in fibromyalgia syndrome.

Selective serotonin reuptake inhibitors (SSRIs) are less effective for neuropathic pain management. For example, fluoxetine decreases pain secondary to diabetic neuropathy, but only in depressed patients. On the other hand, paroxetine was comparable to imipramine for relieving diabetic neuropathy-related pain, independent of mood. In one study, citalopram was more effective than placebo for decreasing diabetic neuropathic pain. More recently, escitalopram was shown to be effective in neuropathic pain, independent of depressed mood. Overall, SSRIs are considered second to third line agents for the management of cancer neuropathic pain.

Anticonvulsants
The anticonvulsants gabapentin and pregabalin are considered first-line therapy for many neuropathies. As with TCAs and SNRIs, there is limited data available about the use of these agents, specifically for cancer neuropathic pain. Other anticonvulsants such as carbamazepine, phenytoin, and lamotrigine can be used to treat neuropathic pain and are considered second line therapies. Carbamazepine and pregabalin are both approved by the FDA for treatment of neuropathic pain. Carbamazepine and other anticonvulsants, such as phenytoin and lamotrigine, work by blocking the sodium channels in an activity-dependent manner. The most common side effects of carbamazepine are dizziness, nausea, vomiting, and dyspepsia. These symptoms are dose-related, and can be minimized by starting with low doses. Carbamazepine has a black box warning for blood
dyscrasias, including agranulocytosis and aplastic anemia. Newer anticonvulsants such as gabapentin and pregabalin are becoming common choices in treating various types of neuropathic pain. Both gabapentin and pregabalin bind to the α2δ subunit of voltage-dependent N-type calcium channels in the spinal nerve terminals of primary afferents and reduce the release of neurotransmitters like glutamate, Substrate P, NE, serotonin, and dopamine. These neurotransmitters are responsible for the transmission of pain signals from primary afferent neurons to the ascending neurons that carry pain signals to the brain. Thus, the analgesic activity of gabapentin and pregabalin is believed to be due to the reduction in release of these neurotransmitters in the dorsal horn of the spinal cord. Pregabalin binds to α2δ receptor with more affinity than gabapentin and is therefore more potent than gabapentin. The effective dose of gabapentin is up to 3,600 mg/day whereas, that of pregabalin is up to 300 mg/day. The pharmacokinetics of pregabalin is more linear than gabapentin and hence its effects are more predictable than gabapentin. The most common side effects associated with gabapentin and pregabalin are asthenia, headache, dizziness and somnolence. Practical disadvantages to consider for the use of pregabalin and gabapentin are multiple daily dosing and relatively expensive cost. Though a generic exists for gabapentin, the cost can still be relatively high due to the high doses often required to treat neuropathic pain.

**Antiarrhythmics**

Certain antiarrhythmics have sodium-blocking activity, making them a consideration for use in neuropathic pain. The most common antiarrhythmic to be used for neuropathic pain is topical lidocaine, specifically the 5 percent patch. Use of the 5 percent lidocaine patch may be limited in cancer neuropathic pain since the patch acts locally with minimal systemic absorption. Since the patch has minimal systemic absorption, side effects tend to be mild local reactions. Low-dose IV lidocaine is sometimes used for temporary pain relief from peripheral nervous system injuries, including diabetic neuropathy and postherpetic neuralgia. Use of parenteral lidocaine should be reserved for resistant cancer neuropathic pain and should be managed by an experienced pain and palliative care team. Mexiletine and clonidine are other considerations for neuropathic pain, though their use is limited by side effects and many other practical considerations.

**TRADITIONAL ANALGESICS**

**Tramadol**

Tramadol is believed to act by a combination of mechanisms, such as weak opioid agonism and NE and serotonin reuptake inhibition. It is tramadol’s active metabolite that binds to the μ-opioid receptor. Only a few small clinical studies have examined the efficacy of tramadol on neuropathic pain. Tramadol should be avoided in patients with a history of seizures or substance abuse. Avoid use in patients with a primary brain cancer or at high risk of metastatic spread to the brain. In addition, there is a risk for serotonin syndrome if given with other serotonergic agents, such as SSRIs, MAO inhibitors, and triptans. The recommended starting dose is 50–100 mg then increase to a maximum dose of 100 mg QID. Lower doses should be used in older patients or patients with either renal or hepatic dysfunction. From a practical consideration, tramadol has a relatively quick onset of action. This makes tramadol a good option for acute/short-term cancer neuropathic pain, a breakthrough agent for exacerbations, or a breakthrough agent while another agent is being titrated to an appropriate dose. A newer, more potent agent with a similar mechanism of action to tramadol is Nucynta® (tapentadol). Up to now, use of this agent for neuropathic pain has been limited.

Neither tramadol or tapentadol are FDA approved for the management of cancer neuropathic pain, thus at this time neither should be routinely recommended for the chronic management of cancer neuropathic pain. As more experience and data are accumulated, use of tapentadol in cancer neuropathic pain could increase.

**Opioids**

Different types of opioid analgesics are used for neuropathic pain relief, although they are not the drugs of choice in neu-
ropathic cancer pain. Their use is also limited because of the high incidence of adverse effects and misuse potential. The pharmacological activity of opioids depends on their affinity for opioid receptor. Drugs such as morphine and methadone are used due to their analgesic affects. Morphine is the drug of choice for severe nociceptive pain. Other medications in this category are oxycodone, hydromorphone, fentanyl, levorphanol, methadone, codeine (though not recommended in pain management because of its low potency and large adverse effect profile), hydrocodone, oxymorphone, and buprenorphine. Meperidine should be avoided in the management of any cancer pain because of the increased risk of delirium and seizures due to the accumulation of normeperidine.

**COMBINATION THERAPY**

The combination of opioid and non-opioid oral analgesics (antidepressants or anticonvulsants) can be used to improve pain relief and reduce side effects. This approach allows for the use of lower doses of opioids and can be particularly effective in managing neuropathic pain.

<table>
<thead>
<tr>
<th>Medication &amp; mechanism of action</th>
<th>Starting dose &amp; maximum daily dosage</th>
<th>Side effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desipramine</td>
<td>S: 25 mg daily; M: 150 mg daily</td>
<td>Anticholinergic effects</td>
<td>Best if given at bedtime to reduce side effects. Active metabolite of imipramine; has the lowest rate of anticholinergic side effects of all TCAs. Use with caution in patients with cardiovascular disease. An FDA approved medication guide must be given to the patient.***</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>S: 10–25 mg daily; M: 75–150 mg daily</td>
<td>Anticholinergic effects</td>
<td>Best if given at bedtime to reduce side effects. Active metabolite of amitriptyline; has fewer side effects than amitriptyline. Use with caution in patients with cardiovascular disease.</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>S: 100–300 mg daily to three times daily; M: 2,400–3,600 mg divided into TID**</td>
<td>Ataxia, dizziness, depression, mood alterations, tremor</td>
<td>Well tolerated. Minimal drug interactions. Caution use in patients with resistant edema. Lower dose required in renal impairment.</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>S: 50 mg TID or 75 mg BID*; M: 300–600 mg divided into BID-TID</td>
<td>Somnolence, dizziness, peripheral edema</td>
<td>Lower dose required in renal impairment. C-V medication to small risk of euphoria.</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>S: 37.5 mg daily to twice daily; M: 75–225 mg given once daily or divided into BID</td>
<td>Nausea, insomnia, constipation/diarrhea</td>
<td>Caution use in cardiac disease. Caution in concomitant use with tramadol. Lower dose required in renal impairment. Avoid abrupt discontinuation – withdrawal can occur.</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>S: 30–60 mg daily; M: 60 mg BID</td>
<td>Nausea, insomnia, constipation/diarrhea</td>
<td>Caution use in hepatic and renal impairment; avoid abrupt discontinuation; caution in concomitant use with tramadol.</td>
</tr>
</tbody>
</table>

*BiD = Twice daily
**TID = Three times daily
***An FDA approved medication guide must be given to any patient receiving an antidepressant or anticonvulsant.

Table 7: Common Antidepressants and Anticonvulsants Used in Neuropathic Pain
vulsants) often results in superior analgesic effects. Affecting multiple receptors at the same time can enhance the pain relief and potentially result in lower doses than if each agent were used alone. A study conducted by Gilron, et al. concluded combination therapy of morphine and gabapentin provided better pain relief than either medication alone or placebo. Another recent study concluded that combination therapy of gabapentin and nortriptyline may provide better pain relief than monotherapy in patients with difficult to manage neuropathic pain. Combination therapy is a consideration for difficult to manage cancer neuropathic pain, but more well controlled studies are needed before its use can be widely recommended.

ALTERNATIVE THERAPIES FOR PAIN MANAGEMENT

Various non-pharmacologic therapies exist for the management of cancer pain in conjunction with pharmacological interventions, although few have been studied with randomized, controlled clinical trials. These alternative therapies may be especially important in pediatric and geriatric populations because standard pharmacological treatment may be less tolerated. Non-pharmacologic approaches for cancer pain management can be categorized into two types: physical modalities and psychological interventions. Physical modalities include patient positioning, physical therapy, massage, acupuncture, application of heat or ice, transcutaneous electrical nerve stimulation (TENS), and ultrasonic stimulation. Psychological interventions include relaxation, meditation, hypnosis, and cognitive behavioral training. Use of non-pharmacologic therapies depends on many factors, including the characteristics of cancer pain (such as pain intensity, duration, and location), patient condition, and patient preference. Pharmacists should be knowledgeable about these alternative pain management approaches and be able to educate patients and refer them to other health care providers to obtain these non-pharmacologic treatments.

CONCLUSIONS

Pain management is an essential component of cancer patient care. With appropriate pharmacologic and non-pharmacologic treatment, both nociceptive and neuropathic cancer pain can be managed well. It is critical for pharmacists to be able to recognize and distinguish common symptoms of nociceptive pain and neuropathic pain. Depending on the pain intensity, non-opioids like NSAIDS and opioids of varying potency can be used to relieve nociceptive pain. For persistent cancer pain, long-acting opioids are most appropriate while there are various novel rapid-acting fentanyl transmucosal products available for managing breakthrough cancer pain. Neuropathic cancer pain treatment options include antidepressants, anticonvulsants, opioids, topical analgesics and combination therapies. With an extensive knowledge of medications, pharmacists are in a prime position to assist in the management of cancer pain by selecting medications to meet the individual needs of cancer patients and improve their health-related quality of life.
Cancer Pain Management
Feb. 2, 2013 (expires Feb. 2, 2016) • Activity Type: Knowledge-based

To earn continuing education credit: ACPE Program
207-000-13-002-H01-P; 207-000-13-002-H01-T
A score of 70 percent is required to successfully complete the C.E. quiz. If a passing score is not achieved, one free reexamination is permitted.

Answer sheet for your use below

CONTINUING EDUCATION QUIZ
Select the correct answer.

1. Identify the possible cause(s) of pain in cancerous tissues.
   a. Pressure caused by tumor expansion
   b. Secretion of inflammatory and pro-hyperalgesic mediators by tumor cells
   c. Down regulation of nociceptors in tumor cells
   d. A and B

2. Which of the following is a sodium channel blocker that is used topically to relieve neuropathic pain?
   a. Capsaicin
   b. Lidocaine
   c. Carbamazepine
   d. Phenytoin

3. Which of the following two TIRF medicines have established conversions?
   a. Onsolis to Fentora
   b. Actiq to Onsolis
   c. Actiq to Fentora
   d. Fentora to Lazanda

4. What is the maximum number of tablets of hydrocodone/acetaminophen 5 mg/325 mg a patient can safely take for a 24-hour period?
   a. six
   b. eight
   c. 12
   d. There is no ceiling dose.

5. Which of the following opioid products may be suitable for managing severe persistent cancer pain for a patient who has trouble swallowing?
   a. Exalgo
   b. Opana ER
   c. Kadian
   d. OxyContin

6. The following statement BEST describes what medication? This medication primarily works by inhibiting serotonin and norepinephrine reuptake, weakly binds mu receptors, and should be used in caution with patients at risk for seizures.
   a. Tramadol
   b. Venlafaxine
   c. Desipramine
   d. Carbamazepine
7. The selection of an appropriate opioid for managing cancer pain depends on which of the following factors:
   a. Cost
   b. Adverse effects
   c. Previous patient responses
   d. All of the above factors

8. VL is a 62-year-old male with a medical history of diabetes, hypertension, and moderate to severe nociceptive chronic pain from colon cancer. Which of the following would be the BEST option to utilize for his chronic pain management?
   a. Morphine
   b. Meperidine
   c. Sublingual fentanyl
   d. Hydrocodone/acetaminophen

9. TP is a 58-year-old male with a medical history of prostate cancer with bone metastases and dyslipidemia. TP is complaining of mild to moderate pain that is worse with movement and is believed to be related to inflammation from the bone metastases. Which of the following would be the BEST option to utilize for TP’s pain?
   a. Fentanyl
   b. Ibuprofen
   c. Duloxetine
   d. Amitriptyline

10. All of the following opioids would be appropriate to recommend for a cancer pain patient with a large opioid requirement EXCEPT:
    a. Fentanyl
    b. Pentazocine
    c. Oxymorphone
    d. Hydromorphone

11. Morphine may not be the best option for moderate to severe cancer pain for the following patient(s):
    a. Unable to swallow
    b. Renal insufficiency
    c. Large chronic doses
    d. Renal insufficiency and large chronic doses

12. All of the following are beneficial properties of methadone when used for cancer pain management EXCEPT?
    a. Mu receptor agonists
    b. NMDA receptor antagonist
    c. Minimal medication interactions
    d. Norepinephrine/Serotonin reuptake inhibitor

13. The following statement describes which side effect of opioids: _________ is the one common side effect of opioids that a patient will not develop tolerance to and is primarily caused via a peripheral mechanism by decreasing the propulsive activity of the intestine and increasing absorption of fluid and electrolytes from the intestine?
    a. Nausea
    b. Pruritus
    c. Sedation
    d. Constipation

14. Which of the following agents is effective at treating nausea and vomiting related to opioids since it has multiple mechanisms of action, including gastrointestinal prokinesis and dopamine blockade? Select the BEST answer.
    a. Haloperidol
    b. Promethazine
    c. Metoclopramide
    d. Prochlorperazine

15. SW is a 64-year-old female patient with a history of chronic pain from multiple myeloma. Until now the patient’s pain has been well controlled on oxycodone. Recently, SW has described his pain as burning, tingling, sharp, and often radiates from her back down to her feet. Which of the following would be the BEST option to treat her pain?
    a. Fentanyl
    b. ibuprofen
    c. Duloxetine
    d. Amitriptyline

16. All of the following agents are considered first line treatment options for cancer neuropathic pain EXCEPT? Select the BEST answer.
    a. Pregabalin (Lyrica®)
    b. Duloxetine (Cymbalta)
    c. Zonisamide (Zonegran)
    d. Nortriptyline (Pamelor)
Cancer Pain Patient Case
Use Table 3 (conservative fentanyl transdermal conversion) from the article to answer this question. VK is a 45-year-old patient with chronic pain from metastatic prostate cancer. Other than chronic pain and prostate cancer, VK is healthy with no other medical history. VK currently has well controlled pain (rates 3/10) while taking morphine extended release 45 mg orally twice daily and morphine immediate release 10 mg q 3 hours PRN pain (he averages three doses per day). VK has heard about a pain patch that only needs to be changed every three days.

17. Please recommend the BEST fentanyl patch strength for VK.
   a. Fentanyl 12.5 mcg patch q 72 hours
   b. Fentanyl 25 mcg patch q 72 hours
   c. Fentanyl 50 mcg patch q 72 hours
   d. Fentanyl 100 mcg patch q 72 hours

At this same visit, VK complains of constipation that he has had since the initiation of the morphine. He only has one to two bowel movements per week (average was 4–5 per week prior to opioid use), and has to strain when he does have a bowel movement. He would like a recommendation for his constipation.

18. Select the BEST option to treat VK’s constipation.
   a. Saline enema
   b. Metoclopramide
   c. MethylNaltrexone
   d. Senna plus docusate sodium

VK comes back to you one year later (no other medical problems other than the cancer and pain) with the regimen that you recommended above. VK is now complaining of a new pain that is sharp, shooting, and burning. This pain starts in his back and radiates down to his legs and feet. He rates his pain at a 5/10 with his goal being a 3/10.

19. Select the BEST treatment option for VK.
   a. Add a Lidoderm® patch
   b. Add Levetiracetam (Keppra®)
   c. Add Gabapentin (Neurontin®)
   d. Increase the scheduled fentanyl patch dose.

Cancer Neuropathic Pain Patient Case:
JF is a 54-year-old female with a history of metastatic breast cancer to her left breast and surrounding axilla. JF is experiencing chronic pain that she describes as a sharp, shooting, knife-like pain in her left breast and shoulder area that radiates down to her left hand. She rates her pain at a 5/10. JF also states that the pain makes it difficult for her to sleep at night. The pain has been non-responsive to both over the counter acetaminophen and ibuprofen. JF’s medical history includes insomnia and hypertension and she is currently between treatment cycles for her breast cancer. Her current medication list is as follows and she has NKDA:
• Hydrochlorothiazide 25 mg orally once daily
• Lisinopril 10 mg orally once daily
• Diphenhydramine 25 mg orally at bedtime as needed for sleep — takes three to four times per week
• Acetaminophen 500 mg orally q four hours as needed for pain — takes once to twice per day
• Ibuprofen 200 mg, takes two tablets orally q four hours as needed for pain — takes once to twice per day

20. Which of the following would be the BEST recommendation to help treat JF’s pain?
   a. Naproxen
   b. Venlafaxine
   c. Desipramine
   d. Oxycodone extended release