

CME Information

Target Audience:

Nurses, pharmacists, and physicians involved in the treatment of cancer patients with pain.

Learning Objectives:

Upon completion of this activity, participants should be able to:

- Describe the pathophysiology and characteristics of breakthrough pain, its prevalence, and the negative impact on patients
- Explain the pharmacokinetics of opioids, benefits and limitations of approved treatments for breakthrough pain, and investigational agents
- Evaluate the concepts of opioid misuse, abuse, and addiction; ways to minimize risk in cancer patients taking opioids; and strategies to address issues, including the implementation of Risk Evaluation and Mitigation Strategy (REMS) programs
- Discuss special considerations for nurses, pharmacists, pain medicine specialists, and oncologists who treat cancer patients with breakthrough pain, and how clinicians can collaborate to improve patient outcomes
- Explore patient case studies in cancer patients in order to promote practical learning

Breakthrough Pain in Patients with Cancer: Essential Concepts for Nursing, Pharmacy, Oncology, and Pain Management Professionals

Introduction and Objectives

Chronic and breakthrough pain are significant problems in patients with cancer. The objectives of this program are to: describe the problem of breakthrough pain and the negative impact on patients; discuss treatment options; evaluate the problem of opioid abuse and addiction, ways to minimize risk, and address issues when they arise; to review special considerations for nurses, pharmacists, pain medicine specialists, and oncologists who treat cancer patients with breakthrough pain; and to explore patient case studies in order to promote practical learning.

Defining Breakthrough Pain

Breakthrough pain is a transitory, flare of pain that occurs on top of a background of otherwise *controlled* persistent pain.[1-3] It is important to note that this definition requires control of the persistent pain; if this is not the case, the entire picture is of uncontrolled pain.

Breakthrough pain can be classified as: 1) incident or provoked (which may or may not be predictable or under the patient's control); 2) idiopathic or spontaneous; or 3) "end-of-dose failure" of a long-acting opioid.[2,3] In terms of characteristics of breakthrough pain, on average, episodes reach peak severity in 3 to 5 minutes, are severe or excruciating in severity, last between 15 and 30 minutes, and occur 1 to 5 times per day.[3]

The Problem of Breakthrough Pain in Patients with Cancer

Epidemiology

Pain is a common occurrence in patients with cancer. Patients experience pain at all disease stages and it can be present for an extended time and thus become chronic.[3] Estimates suggest that 60% to 90% of patients with advanced cancer experience significant pain that can be attributable to the disease itself or treatment.[4-10]

Breakthrough pain is also a significant problem in cancer patients. It has been estimated that between 65% and 85% of patients with cancer experience breakthrough pain.[11-15]

Recent results from the European Pain in Cancer (EPIC) Survey, the largest study investigating the prevalence, treatment, and impact of cancer-related pain, exemplify the problem of pain in cancer patients. Key results from the study are the following[16]:

- 56% of patients experienced moderate-to-severe pain at least monthly
- 63% of patients taking prescription pain medication reported experiencing breakthrough pain or inadequate pain relief
- 69% of patients reported having difficulties with everyday activities due to their pain

Quality of Life Implications

Unmanaged pain has a negative impact on both patients and their families. Appetite, sleep, and emotional well-being are just a few daily functions that are affected. Importantly, patients with breakthrough pain experience more significant problems than those without breakthrough pain; for example, they have greater psychological distress and higher economic burden.[12,13,17,18]

Pharmacologic Management of Breakthrough Pain: Focus on Opioids

Treatments to be considered include pharmacologic therapies such as NSAIDs, opioids, anticonvulsants, and norepinephrine reuptake inhibitors; and procedural options such as simple nerve blocks with or without steroid injections, radiofrequency or chemical denervation, central or peripheral neurostimulation, or intrathecal infusion therapy. Other treatments that may be warranted include surgical debulking or radiation therapy; heat or ice application; wraps/braces/corsets, physical and massage therapy; and pacing activities.

In terms of pharmacotherapy, opioids are most commonly used to treat breakthrough pain. The three different classes of opioids are: long acting, short acting, and rapid onset. Table 1 shows the FDA-approved drugs within the classes.

Table 1. Opioid Classes

| Long Acting Opioids | Short Acting Opioids | Rapid Onset Opioids |
|----------------------------------|-----------------------------|---|
| Fentanyl transdermal system | Codeine | Oral transmucosal fentanyl citrate (OTFC) |
| Methadone/buprenorphine | Hydrocodone | Fentanyl buccal tablet (FBT) |
| Morphine, oxycodone, oxymorphone | Hydromorphone | Fentanyl buccal soluble film (FBSF) |
| Levorphanol | Morphine | |
| Tramadol | Oxycodone | |
| | Tramadol | |
| | Tapentadol | |

Opioids that are most often used to treat breakthrough pain include morphine, hydromorphone, hydrocodone (with acetaminophen), oxycodone (with or without acetaminophen), oxymorphone, methadone, and fentanyl. Fentanyl is the most lipophilic drug, hence the fastest onset of analgesia.

In general, rapid onset opioids best match the characteristics of breakthrough pain so they are ideal treatments. These features include:

- A rapid onset of analgesia, within minutes
- A durable response
- An ability to sustain pain relief for up to 30 minutes
- An ability to combine well with ATC medications
- Ease of use for patients
- Flexible dosing
- An ability to easily adjust the dose

There are currently 3 approved rapid onset opioids: OTFC, FBT, and FBSF. FBSF was approved in 2009 and is the newest member of the class. FBSF is a film that is placed inside of the cheek that contains a water-erodible polymer inactive layer and a bioadhesive water-erodible mucoadhesive drug layer. Other drugs such as aerosolized liposome-encapsulated fentanyl, sublingual fentanyl, and fentanyl nasal spray are under investigation. New technologies such as these were developed to provide improved pharmacokinetics, more flexible dosing, more consistent dosing, improved tolerability, and other features not present in earlier generation drugs.

Table 2 compares the 3 approved rapid onset opioids.

Table 2. Comparison Between Rapid Onset Opioids[19-23]

| Parameter | FBSF | FBT | OTFC |
|----------------------------------|-----------------|----------------------|-----------------|
| Absolute Bioavailability | 71% | 65% ($\pm 20\%$) | 47% |
| Fraction Absorbed Transmucosally | 51% | 48% ($\pm 31.8\%$) | 22% |
| T _{max} 800 µg (min) | 60 (45-240) | 40 (25-180) | 25 (20-120) |
| C _{max} 800 µg (ng/mL) | 1.67 \pm 0.75 | 1.59 \pm 0.90 | 1.26 \pm 0.41 |
| AUC (hr·ng/mL) | 14.46 \pm 5.4 | 9.05 \pm 3.72 | 4.79 \pm 1.96 |

Expert Perspectives on Treatment

Oncologist Point of View

In cases of either widely disseminated disease involving multiple sites of metastasis, or in cases of a specific site that is the dominant metastatic focus, breakthrough pain syndromes can be multiple, mixed and complex in origin, and temporal in nature. Thus, patients could have a flare from bone disease, provoked by activity, for example and have a flare from visceral disease, which can occur spontaneously, all at the same time, or spaced out during the day. It is therefore of utmost importance to match breakthrough pain flares to the type of metastatic process that is the cause. In this way, techniques to either pharmacologically manage the pain more optimally, or stabilize areas of metastatic involvement with targeted interventions, such as radiation therapy or ablative techniques, can be added to treatment planning.

It can be very useful to recommend that the patient or family member keep a detailed pain journal of what a typical day is like for the patient. Breakthrough pain is frequently under-treated/under-dosed or eventually can result in the patient's re-admission to the hospital for intractable pain when dosing and drug selection do not match the syndrome. Indeed, it has been observed that when patients are discharged from the hospital, compliance with around-the-clock medication is far better than with breakthrough medication, and the lack of adequate instruction in using breakthrough medication is primarily responsible for poor outcomes in controlling pain a week or two post-discharge. This is also the case in outpatient situations where breakthrough pain is being monitored and managed in patients who have increasing pain issues.

A simple arithmetical relationship to correct dosing is also useful to describe as a way to limit these problems. The correct breakthrough dose for short acting opioids (ie, morphine, oxycodone, or hydromorphone) is between 10 and 20 percent of the total dose of opioid received in a 24 hour period in the tolerant patient. So, if a patient is receiving a total of 120 mg of long acting morphine per day, the correct dose of morphine equivalent to treat each episode of breakthrough pain is going to be about 15 mg per dose, every 2-4 hours as needed.

When a rapid onset drug is used, the starting dose should NOT be calculated in this way, but individually titrated per patient, starting at the lowest possible dose first, and titrating up over a few days of evaluation as necessary.

It is important to emphasize that if the pattern of breakthrough pain is more than 3 or 4 episodes per day, the patient is at risk for developing unstable pain or worse, a pain crisis, which is the usual reason for hospital admission. In most cases, if the disease is under control this should not happen with appropriate management. If the disease is not well controlled, it is necessary to determine which metastatic process is primarily responsible, and efforts to stabilize that situation will more rapidly help solve the problem. The challenge is to recognize the syndrome, match it, and treat aggressively to "cure" the patient of pain. This is a highly desirable and achievable goal in most cases.

Pain Specialist Point of View

When assessing patients with a diagnosis of cancer in regard to issues with breakthrough pain, it is incumbent upon the physician to thoroughly evaluate the patient and attempt to arrive at a specific diagnosis for the pain complaint. Too often, treatments are offered for symptom management, but with little understanding of the actual processes taking place. Understanding the mechanisms and anatomy involved will lead to the creation of a more cohesive treatment plan.

In this population it is important to distinguish between tumor-related pain, pain that results from treatment of the disease (surgery, chemotherapy, or radiation therapy), or pain from a condition unrelated to the cancer diagnosis (arthritis, routine low back pain, etc). This has implications as to the mechanisms involved. In addition, it is important to perform a detailed neurological exam to determine which neural pathways are involved with the origin and maintenance of the pain complaint. These factors will aid the physician in selecting an array of multimodal treatments that will be complementary in order to optimize the outcome.

Pharmacist Point of View

There are several considerations when selecting the best opioid to manage breakthrough pain, and onset of analgesia is probably one of the most important. For example, if a patient is experiencing primarily volitional incident pain (e.g., pain that has a clear precipitating event that is under the patient's control such as walking, wound care, therapy, etc.) it would be reasonable to use morphine or oxycodone, and premedicate 45-60 minutes before the pain-evoking event. One guideline is to give 10-15% of the total daily dose of the opioid used for the baseline or persistent pain for breakthrough pain.

On the other hand, if the patient is experiencing idiopathic or spontaneous pain, the choice of opioid would be determined by how quickly the pain evolves. If the pain takes 30-60 minutes to worsen, the patient can self-administer one of the more water-soluble opioids such as morphine, oxycodone, or hydromorphone, whose onset of action is about 30 minutes. On the other hand, if the pain is fairly abrupt in onset, it would be preferable to use an opioid with a quicker onset of analgesia such as methadone or fentanyl. In choosing between these two opioids, it is important to recognize that methadone has a fairly long terminal half-life and will have a duration of effect of up to six hours. Transmucosal fentanyl products offer quick onset of analgesia, as well as a short duration of effect (1-2 hours).

Other variables that must be considered when selecting an opioid are the patient's age, organ status (liver and renal), ability to swallow, preferences, and healthcare beliefs. Matching the onset of action and duration of effect of the opioid with the presentation of the pain is a reasonable first step.

Pharmacists are in an excellent position to work with prescribers to select the best opioid to treat patient-specific breakthrough pain. After selecting the best opioid for a given patient, the pharmacist can provide initial dosing information, and guidance on titration. Pharmacists are also frequently called on to perform opioid conversion calculations, an intervention commonly employed when caring for cancer patients with pain.

Oncology Nurse Point of View

There are six critical strategies for BTP management. First, the professional nurse must examine and understand personal biases in the area of pain, pain management and addiction and one's personal phobias of opioids. Personal biases can interfere with rapport building and can create obstacles to diagnosis and treatment of the patient. The role of professional nurses is to serve the patient without regard to race, ethnicity, gender, or condition. Without vigilance, our biases can turn us into judge and jury.

The second strategy is to thoroughly assess the patient's physical condition and the pain. Such assessment parameters as pain duration, onset, and intensity; aggravating factors; relieving factors; previous pain experiences; pain beliefs and patient/caregiver fears; as well as risk for misuse, abuse, and addiction; lay the foundation for a successful pain management plan. If pain assessment tools such as the Brief Pain Inventory are utilized, ensure that these are used consistently throughout the patient's treatment course.

The next critical strategy is education of the patient and caregiver in the care requirements for successful pain management. This could include medication information, instruction on side effect reporting and management, training on non-pharmacologic techniques, and the importance of compliance with the treatment plan.

The backbone of the nursing process as well as successful breakthrough pain management is reassessment of the patient's response to the treatment and evaluation of treatment plan for effectiveness. This reassessment includes the same components as the initial assessment with emphasis on the response to medication and non-pharmacologic interventions. Again, risk of misuse, abuse, and addiction must be evaluated. A thorough reassessment leads to further fine-tuning of the treatment plan.

Two strategies that truly impact the whole process of successful pain management are collaboration with other members of the healthcare team and building of the nurse-patient relationship. Collaboration, like pain assessment and management, is a process, not an event. Collaboration with other members of the healthcare team is paramount to achieving an acceptable pain relief level for the patient. Often there are divergent opinions regarding the care of a patient and collaboration focuses on trying to reach agreement so that patient goals can be achieved. Along with expertise in the area of pain and pain management, collaboration with other health professionals mandates knowledge of the patient's goals and the patient's condition.

The last strategy, which is inherent in the nursing role, is the building of rapport with the patient and his or her caregivers. Rapport is built from words, tone, body language, preparation, compassion, and an honest desire to improve the patient's predicament of pain.

Barriers to the Treatment of Breakthrough Pain: Focus on Concerns about Abuse, Addiction, and Diversion and Ways to Reduce Risk and Improve Treatment Outcomes

As described above, a number of factors such as personal biases in the area of pain, pain management, and addiction, and personal phobias of opioids, have an impact on the treatment of breakthrough pain. Table 3 lists these some of the barriers to effective pain management.

Table 3. Barriers to Effective Pain Management[24]

| Healthcare Providers | Patients | Healthcare System |
|--|---|---|
| Inadequate knowledge of pain management | Reluctance to report pain | Low priority given to cancer pain treatment |
| Poor assessment of pain | Concern about distracting physicians from treatment of underlying disease | Inadequate reimbursement |
| Concern about regulation of controlled substances | Fear that pain means disease is worse | The most appropriate treatment may not be reimbursed or may be too costly for patients and families |
| Fear of patient addiction | Concern about not being a "good" patient | Restrictive regulation of controlled substances |
| Concern about side effects of analgesics | Reluctance to take pain medications | Problems of availability of treatment or access to it |
| Concern about patients becoming tolerant to analgesics | Fear of addiction or being thought of as an addict | Opioids unavailable in the patient's pharmacy |
| | Worries about unmanageable side effects | |
| | Concern about becoming tolerant to pain medications | |
| | Poor adherence with the prescribed analgesic regimen | |

According to results from a meta-analysis, pain is undertreated in nearly half of cancer patients.[25] Results from one survey showed that only 25% of patients with breakthrough pain are satisfied with pain control compared to 78% of patients without breakthrough pain.[12] The following recently reported results from the EPIC study also support the fact that pain is undertreated and that significant barriers are involved[16]:

- 50% of patients believed that their quality of life was not considered a priority in their overall care by their health care professional
- 38% of patients said they believe that their clinician would rather treat their cancer than the accompanying pain
- 33% of patients said that their clinician does not have time to discuss pain
- 26% of patients said that their clinician did not know how to treat moderate-to-severe cancer pain

With these barriers and their negative impact on treatment in mind, there clearly is a need to improve knowledge and to address these barriers to help improve treatment outcomes.

Expert Perspectives on Abuse and Addiction

Addiction Specialist Point of View

Importantly, the definition of addiction in medically ill patients must take into account the fact that these patients receive potentially abusable drugs for legitimate medical purposes. With this in mind, an appropriate definition of addiction for cancer patients is: "a chronic disorder characterized by the compulsive use of a substance resulting in physical, psychological or social harm to the user and continued use despite that harm." [26]

In order to identify problems in the clinical setting it is necessary to extend this definition to include the signs of aberrant drug-related behavior. Aberrant behavior can be attributed to true addiction (substance dependence); however, other alternative explanations are possible. For example, pseudoaddiction must be considered if the patient reports distress associated with unrelieved symptoms, and impulsive drug use may be indicative of another psychiatric disorder. In addition, the degree of aberrancy can help with the identification of true addiction. Less aberrant behaviors (such as aggressively complaining about the need for medications) are more likely to reflect untreated distress of some type, rather than addiction. Conversely, the more aberrant behaviors (such as injection of an oral formulation) are more likely to reflect addiction.

Aberrant drug-taking among cancer patients with or without a prior history of substance abuse is a serious and complex clinical occurrence. Whether the patient is an active drug abuser, has a history of substance abuse, or is not complying with the therapeutic regimen, the clinician should establish structure, control, and monitoring. A multidisciplinary team approach is optimal. If possible, mental health professionals with specialization in addiction can be instrumental in developing strategies for management and treatment compliance.

Successful identification and management of aberrant drug behaviors involves 3 steps: 1) assessment; 2) development of a treatment plan; and 3) monitoring.

1) Assessment

The first member of the medical team to suspect problematic drug-taking or a history of drug abuse should alert the patient's healthcare team. A physician should assess the potential of withdrawal or other pressing concerns and begin involving other staff (ie, social work and/or psychiatry) to assess management strategies. Obtaining as detailed a history as possible is critical. Frequently, clinicians avoid asking patients about substance abuse because they fear that they will anger the patient or that their suspicion of abuse is incorrect. The use of a careful, graduated interview approach is effective at slowly introducing the assessment of drug use. This entails beginning with broad questions about the role of drugs (eg, nicotine, caffeine) in the patient's life, and gradually becoming more specific in focus to include illicit drugs. Importantly, screening questionnaires such as the Opioid Risk Tool or the Screener and Opioid Assessment for Patients in Pain, or the Pain Assessment and Documentation Tool (PADT) which can be used to screen and monitor ongoing behaviors, can be used.[27,28] The PADT focuses on the "Four A's" of pain management: Analgesia, Activities of Daily Living, Adverse side effects, and potentially Aberrant Drug-taking Behaviors.

2) Development of a Treatment Plan

When developing a treatment plan it is first essential to outline clear treatment goals. In some cases, complete remission of the substance abuse problem may not be reasonable due to the distress of coping with a serious illness. In that case, "harm reduction", with the goal of enhancing social support, maximizing treatment compliance, and containing harm through episodic relapse, may be more feasible. The following aspects are important to consider when developing a treatment plan:

- Establishing a relationship with the patient that is based on empathic listening
- Utilizing non-opioid and behavioral interventions when possible, but not as substitutes for appropriate pharmacologic management
- Considering tolerance, route of administration, and duration of action when prescribing medications for pain and symptom management. The use of medications with slow onset and longer duration may help reduce the risk of aberrant behaviors in patients with addictive disorders
- Frequently reassessing the adequacy of pain and symptom control

3) Patient Monitoring

Clinicians are responsible for controlling and monitoring drug use in all patients. Unfortunately, substance abuse may even shorten life expectancy by preventing the effective administration of primary therapy. In addition, prognosis may also be altered if abused drugs negatively interact with therapy or predispose the patient to experience other serious morbidities.

Urine toxicology screening should be employed both for diagnosing potential abuse problems and for monitoring patients with a history of abuse. An additional strategy for promoting appropriate drug use in outpatients is to incorporate a written contract between the pain

management team and the patient that may include: spot urine screens, expectations regarding clinic visits and medication dispensed, and requirements for attending programs such as 12-step programs. Additional strategies for inpatients include: discussing the patient's drug abuse openly; reassuring the patient that adverse events such as drug withdrawal will be avoided whenever possible; admitting patients several days in advance of surgery to stabilize the drug regimen; providing a private room near the nurses' station to promote constant monitoring and to discourage the patient from leaving the hospital to obtain drugs; and requiring visitors to check in with nursing staff prior to visiting the patient to prevent the patient's access to drugs.

Patients in recovery for drug abuse should receive non-opioid therapy where possible. If opioids are needed, it may be necessary to structure opioid use with opioid management contracts, urine toxicology screens, and pill counts; and to maintain close involvement with the patient's recovery program sponsor.

The guidelines above describe some important strategies for patients with cancer who demonstrate aberrant drug-related behavior. Addressing this significant problem requires a comprehensive approach that takes into consideration all aspects of substance abuse and addiction, and that provides practical tools to help manage risk, treat pain effectively, and assure patient safety.

Oncology Nurse Point of View

How Do I Contend With Nursing Or Physician Peers Who Label Patients As Addicts or Drug Abusers?

My first recommendation is to make a solid personal commitment to not accept the labels given to patients until proven otherwise. That "proof" is achieved through thorough, detailed and consistent assessments carried out without bias. Knowledge of pseudoaddiction is critical to examining patient behaviors. For example, frequent requests for opioid medications could represent a behavior in the addicted patient, the patient who is misusing opioids, or the patient who is genuinely seeking pain relief. I would also recommend collaboration with addiction or pain specialists who can provide objective expertise for this patient population.

Pain Specialist Point of View

Often there are concerns in regard to pharmacologic therapy and issues such as diversion and abuse of opioids. It is important to recognize that this happens in the cancer population just as it happens with other chronic pain patients. The patient may share medication with friends and family members, consume inappropriate amounts, sell medication, and also develop behavior problems upon exposure to these medications. Therefore, it would be feasible to employ a consistent approach with all patients utilizing random urine testing, assessment of risk factors from the patient's family, and ongoing follow-up. General principles should be followed such as using an opioid-sparing strategy with NSAIDs, AEDs, and NE-reuptake inhibitors, and using around-the-clock therapy when opioids are required. This will hopefully provide a consistent level of analgesia, reduce reinforcement of pill-taking behavior, and keep flare-ups of pain that require additional medication to a reasonable frequency (1-2 times per day). This should then reduce concern on the part of the clinician that a request for additional breakthrough medication is a drug-seeking behavior, and rather a reasonable request to address legitimate

fluctuations in the level of pain, whether it is attributable to increased activity, from a bone fracture, or from another change in the patient's condition.

The Role of Risk Evaluation and Mitigation Strategies (REMS)

One additional consideration of importance to the topic of abuse and addiction is the recent implementation of Risk Evaluation and Mitigation Strategies (REMS) for new opioids coming to market. REMS are FDA-mandated management strategies to prevent serious risk of a drug and to ensure that appropriate patients receive a drug. With REMS, risks to both the patient and healthcare provider are taken into consideration. REMS can include[29]:

- A Medication Guide
- A Patient Package Insert
- A communication plan
- Elements to assure safe use in appropriate patients
- An implementation system

REMS elements to assure safe use of opioids are the following[29]:

- Healthcare providers who prescribe the drug have particular training or experience, or are specially certified
- Pharmacies, practitioners, or healthcare settings that dispense the drug are specially certified
- The drug is dispensed to patients only in certain healthcare settings, such as hospitals
- The drug is dispensed to patients with evidence or other documentation of safe use conditions, such as laboratory test results
- Each patient using the drug is subject to certain monitoring or each patient using the drug is enrolled in a registry

The ultimate goal of REMS programs is to both protect patients and their healthcare providers; however, in order to ensure that treatment of patients is not negatively affected it is important for both patients and healthcare providers to be educated about the processes and procedures and for any potential issues to be addressed. Questions that may arise that should be addressed may include the following:

- Will patient access to pain medications be reduced?
- Will prescribers avoid prescribing medications with REMS?
- Will costs of pain medication increase?
- Will greater regulation prevent the development and availability of new opioids in the future?

Case Studies in Breakthrough Pain: Practical Learning by Example

Case 1

Background, Symptoms, and Treatment History

A 64-year-old black male with a history of pancreatic cancer presents for consultation with severe abdominal pain. The patient is s/p neoadjuvant chemoradiation and a Whipple procedure in 2008 and presented with a recurrence this past month.

He developed poorly localized diffuse abdominal pain as part of his symptom complex during the recent recurrence, and describes both a chronic underlying persistent pain associated with unpredictable flares of severe pain that can last for 1-2 hours at a time, several times during the day, not controlled with his current pain medication, which consists of acetaminophen 325mg and hydrocodone 10 mg; 1-2 tablets every 4 hours as needed, and a transdermal fentanyl patch of 25 mcg per hour.

He is depressed and fatigued and has lost 12 lbs in the past 6 weeks. He is intermittently nauseous and is severely constipated. Pertinent physical exam reveals a thin black man in mild distress. Sclera is anicteric, abdomen is scaphoid with slightly diminished bowel sounds. There are no palpable masses. CT scan of abdomen is remarkable for numerous liver metastasis, and an overt large tumor mass encompassing a deformed region of the superior mesenteric artery, along with several enlarged periportal lymphnodes. He states that his main complaint is the pain, which prevents him from eating and interrupts his daily activities, as well as any semblance of normal sleep. He rates his average pain at a 7/10 and his flares of pain as 10/10, which are especially severe in the evening, occur without warning, and can last from 30 min to 2 hours or longer, especially at night before sleep.

A prolonged discussion with his physician and family has taken place and the patient has decided to forgo any palliative chemotherapy. He understands his limited prognosis and indicates a desire to be made as comfortable as possible for the time he has left, but states that his pain medication is not helpful.

Key Points and Treatment Recommendation

This patient has advanced pancreatic cancer with polysymptomatology common at this stage. His pain syndrome is a complex cancer pain syndrome best described as a mixed type, with both visceral and neuropathic (plexopathy) features. He describes both a chronic persistent and breakthrough pain pattern typical of visceral pain, which is characterized by a spontaneous idiopathic onset, not usually provoked by movement or a specific episode. It is poorly localized and usually rated as severe. The neuropathic component of pain typically is worse at night.

Given his high pain score, the minimum effective dose of narcotic medication would be at least twice as much as he is currently taking, in order to achieve a desired goal of a 50 percent or greater reduction of both his chronic pain and breakthrough pain scores. Given the acute onset of his breakthrough pain, targeting the episode by selecting an opioid with a rapid onset of action would be an important consideration, and his overall advancing debility would not support the use of acetaminophen containing drug combinations under any circumstance.

Case 2

Background, Symptoms, and Treatment History

The patient is a 51-year-old black male with history of prostate cancer that has metastasized to his bones, who is currently receiving docetaxel based chemotherapy with some mild improvement in his symptoms and lowering of his PSA from 1,240 to 135.

He states he has on occasion severe and unrelenting pain to his pelvis, right groin, lower back, and left-sided chest wall region partly controlled with transdermal fentanyl 400 mcg per hour. Pain is more intense when provoked by movement for which the patient has been taking oxycodone 15-30 mg every 4 hours as needed.

Extent of disease is confirmed by skeletal survey and bone scan, showing multiple areas of metastatic sclerotic lesions. He is notoriously non-compliant with his pain medication and frequently calls at the last minute either right before a weekend or after hours, to request more pain medication. He "eats a boatload" of oxycodone on any given day, more than is prescribed. He calls several physicians separately in the group to renew fentanyl, and has presented himself to the ER twice in the past 3 weeks, stating that he is "in withdrawal" because his prescriptions ran out early.

Two weeks before his next scheduled visit, a prescription for 360- 15 mg tablets of oxycodone IR was given to the patient, with the expectation that he would use approximately 12 per day for his frequent breakthrough episodes. He arrives at the office without an appointment 2 weeks early stating that he is out of the oxycodone and that he took his last pills the night before. He has on 6- 100 mcg of fentanyl patches, many of them hanging off his skin. He refuses an opioid rotation to methadone, stating he is not a "drug addict". His behavior is somewhat labile, and he appears to be agitated.

A urine sample for toxicology is obtained with the patient's consent, which later revealed no oxycodone in his system, but was positive for traces of cocaine and marijuana. When confronted with the results, the patient states he takes so many pills and is in so much pain he lost track of the last time he took them. When liquid morphine concentrate was recommended as a possible alternative to oxycodone, the patient refused, stating that he tried it before and it did "nothing" to help his pain.

Key Points and Treatment Recommendation

The patient clearly has a legitimate cancer pain syndrome typical of metastatic prostate cancer: chronic persistent pain that partially improved with effective systemic chemotherapy, but lingering and recurrent breakthrough pain related to still unstable disease burden in specific well localized areas that even correlate with imaging studies. The patient's behavior pattern is clearly aberrant, with non-compliance, staff splitting, and specific drug preferences typically seen in pseudoaddiction, where these behaviors are more based on ineffective analgesia. The issue of his urine toxicology results, however, demonstrates a disturbing potential problem of substance abuse and diversion. Since oxycodone was prescribed in high amounts but not found on toxicology, this patient's behavior pattern must be looked upon with a high degree of suspicion.

Case 3

Background, Symptoms, and Treatment History

The patient is a 55-year-old grandmother and retired school teacher presenting with a 6 week history of increasing back pain. When the pain became unbearable and not responsive to OTC medication, she went to the emergency room where 2 pathologic compression fractures were noted at T 8 and 9. An MRI showed more extensive spinal disease throughout the vertebral spine with no cord compression, and further work-up revealed multiple myeloma as the diagnosis, with an IgG paraprotein spike.

The patient was admitted and prescribed high dose steroids and radiation therapy. She was then treated with induction chemotherapy and achieved a partial remission, and a bone marrow transplant was being contemplated. She complains of persistent spine/back pain, which limits her movement and function.

She is very anxious and concerned about her condition, as she is the primary caretaker of a semi-invalid husband and cannot afford to privately hire supplemental care. In addition, she babysits her 2 year old grandchild 3 days per week, 4 hours per day, a necessary responsibility to enable her son and daughter-in law to work full time, which helps with overall household financial support for both families.

Her current medications, after detailed and successful titration of her medication, include methadone 20 mg, 3 times per day and tizanidine 2 mg, 3 times per day. She has movement provoked pain which occurs with bending and lifting, and these breakthrough episodes occur at least 5 or 6 times per day. She has tried many short acting medications, but the only one that seems to work best is FBT, 400 mcg every 4 hours as needed for these episodes.

Key Points and Treatment Recommendation

This case highlights the fact that even with successful remittive therapy, chronic and somewhat problematic pain syndromes can and will persist in many malignant states responding to primary therapy, especially when the skeletal system is involved and has been damaged. This leads to survivorship issues, of which care-giving and socioeconomic problems can persist and require an ongoing and frequently interdisciplinary approach to best achieve the optimum result.

Case 4

Background, Symptoms, and Treatment History

The patient is a 56-year-old white female with a recent history of progressive "triple negative" breast cancer with predominant osseous and pulmonary metastatic disease. She is s/p bilateral mastectomy 3 years ago and has had radiation to her left chest wall and upper thoracic spine. She currently receives palliative chemotherapy with capecitabine on a daily basis every 2 weeks and is feeling somewhat better overall, with a decrease in the pain she has in her ribs, and an improvement in her baseline shortness of breath.

An avid gardener and bike rider, she wants to resume some of her activities, but has significant pain on twisting, bending, or pedaling. The pain is localized to her lower back, comes suddenly with activity, and can be severe and last for 1-2 hours. Although the chemotherapy has allowed her to cut down on her use of a fentanyl transdermal patch from 75 mcg per hour to 25 mcg per hour, her pain flares can be severe; on average 8 on a scale of 10. This has impacted her functionality to the point where she fears moving very much and stays home all of the time. She is depressed as a result.

The medication that she was prescribed for breakthrough pain -- oxycodone 5 mg with acetaminophen 325 mg 1-2 tabs every 4 hours as needed -- takes too long to work, upwards of an hour and doesn't "catch" the episodes when they happen, sometimes 5 or 6 times per day. She then feels lethargic and more depressed at the end of the day. She wants to know if there is a medication that acts faster and that is more effective for her "pain flares" and that can allow her to have a better quality of life.

Physical exam reveals a thin w/f in no acute distress, there is mild point tenderness throughout the thoracic spine with mild paravertebral spasm. Plain film X-rays are unremarkable except for slight mottling from T-3-10. MRI of the spine reveals almost complete replacement of multiple vertebral bodies with tumor, but no cord compression. Neurologic exam is non-focal.

The patient has no prior medical or psychosocial history of note, except that she prefers to not take medication if at all possible.

Key Points and Treatment Recommendation

This patient is suffering from a typical type of cancer breakthrough pain. Although the chronic persistent component of her pain is improved with chemotherapy, the breakthrough component, which is related to her spinal disease, has broken through both chemotherapy and radiation. Improvement and maintenance of a satisfactory functional status is of particular importance to this patient, and is the focus of any goals of care discussion. In addition to continuing her current chemotherapy, which is pharmacologically based, this patient is at risk for inadequate treatment or undertreatment. Use of a faster acting opioid preparation may be an optimal choice here, either by way of an intravenous pump or a rapid onset oral opioid. It is likely that a consultation with an anesthesiologist skillful in interventional techniques, such as spinal cord stimulation and/or epidural nerve blockade/anti-inflammatory therapy, may better address her issues of unstable breakthrough pain with concomitant paravertebral spasm.

Case 5

Background, Symptoms, and Treatment History

A 59-year-old emergency room physician presents for pain consultation. He has a diagnosis of metastatic lung cancer with diffuse osseous and pleural based involvement. He is currently receiving chemo-biologic therapy with little improvement in his pain. He describes 2 separate types of pain: the first type is centered in his right hip and lower back, and is exacerbated by

walking, forcing him to use a cane; the second type of pain he experiences on his left side when he coughs, twists his upper body, or exerts himself.

Although he can predict what provokes his pain at times, he frequently has acute flares of both types of pain, and his current medication regimen is ineffective, comprised of oxycodone 15 mg, 1-2 tabs prn and a transdermal fentanyl patch, 100 mcg per hour. His average pain score is 6/10 and his current pain score is 8/10. He was having a flare of pain during his exam, having traveled across a bridge and being stuck in traffic for 30 minutes. Other medical issues include him being a diabetic on oral medication. He refuses to take steroids to help control his pain. The patient is a high-achieving individual with many administrative, clinical, and teaching responsibilities. He insists on continuing work and wants to feel more in control of his symptom burden.

Key Points and Treatment Recommendation

Patients with multiple sites of metastatic cancer frequently have a complex and mixed type of breakthrough pain pattern. In this case, the patient has both visceral and osseous involvement, making his history problematic in deciding which pain is more effectively treated. A combined modality approach using external beam radiation, radiopharmaceutical agents, and bisphosphonates may help "spare" the patient an excessive use of opioid based therapy. In addition, a rotation to a different analgesic regimen may provide additional assistance in maintaining functionality and compliance with primary anti-cancer therapy.

Conclusion

Unmanaged breakthrough pain is a significant problem in cancer patients that has serious implications. To maximize clinical outcomes, an individualized approach to management is required, and risks and benefits of treatment need to be frequently assessed. Emphasis on education about breakthrough pain and its management, and collaboration between nurses, pharmacists, oncologists, pain medicine specialists, and other clinicians will help ensure effective pain management and reduce unnecessary complications for both patients and their healthcare providers.

References

1. Mercadante S, Radbruch L, Caraceni A, et al. Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care. *Cancer*. 2002;94:832-839.
2. Svendsen KB, Andersen S, Arnason S, et al. Breakthrough pain in malignant and non-malignant diseases: a review of prevalence, characteristics and mechanisms. *Eur J Pain*. 2005;9:195-206.
3. Bennett D, Burton AW, Fishman S, et al. Consensus panel recommendations for the assessment and management of breakthrough pain: Part I Assessment. *P&T*. 2005;30(5):296-301.
4. Daut RL, Cleeland CS. The prevalence and severity of pain in cancer. *Cancer*. 1982;50:1913-1918.

5. Cleeland CS. The impact of pain on the patient with cancer. *Cancer*. 1984;54:2635-2641.
6. Foley KM. The treatment of cancer pain. *N Engl J Med*. 1985;313:84-95.
7. Peteet J, Tay V, Cohen G, MacIntyre J. Pain characteristics and treatment in an outpatient cancer population. *Cancer*. 1986;57:1259-1265.
8. Donovan M, Dillon P, McGuire L. Incidence and characteristics of pain in a sample of medical-surgical inpatients. *Pain*. 1987;30:69-78.
9. Greenwald HP, Bonica JJ, Bergner M. The prevalence of pain in four cancers. *Cancer*. 1987;60:2563-2569.
10. Portenoy RK. Cancer pain. Epidemiology and syndromes. *Cancer*. 1989;63:2298-2307.
11. Portenoy RK, Hagen NA. Breakthrough pain: definition, prevalence and characteristics. *Pain*. 1990;41:273-281.
12. Portenoy RK, Payne D, Jacobsen P. Breakthrough pain: characteristics and impact in patients with cancer pain. *Pain*. 1999;81:129-134.
13. Caraceni A, et al; Working Group of an IASP Task Force on Cancer Pain. *Palliat Med*. 2004;18:177-183.
14. Fine PG, Busch MA. Characterization of breakthrough pain by hospice patients and their caregivers. *J Pain Symptom Manage*. 1998;16:179-183.
15. Hwang SS, Chang VT, Kasimis B. Cancer breakthrough pain characteristics and responses to treatment at a VA medical center. *Pain*. 2003;101:55-64.
16. Breivik H, Cherny N, Collett B, et al. Cancer-related pain: a pan-European survey of prevalence, treatment, and patient attitudes. *Ann Oncol*. 2009;20:1420-1433. Epub 2009 Feb 24.
17. Fortner BV, Okon TA, Portenoy RK. A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain. *Pain*. 2002;3:38-44.
18. Bruera E, Schoeller T, Wenk R, et al. A prospective multicenter assessment of the Edmonton staging system for cancer pain. *J Pain Symptom Manage*. 1995;10:348-355.
19. Data on file. MEDA Pharmaceuticals, Inc.
20. FENTORA[®] (fentanyl buccal tablet) prescribing information. Cephalon, Inc., Frazer, PA: 2007.
21. ACTIQ[®] (fentanyl citrate) prescribing information. Cephalon, Inc., Frazer, PA: 2007.
22. Darwish M, Kirby M, Robertson P Jr, Hellriegel E, Jiang JG. Absolute and relative bioavailability of fentanyl buccal tablet and oral transmucosal fentanyl citrate. *J Clin Pharmacol*. 2007;47:343-50.
23. Webster LR. Fentanyl buccal tablets. *Exp Opin Investig Drugs*. 2006;15:1469-1473.
24. Pain (PDQ[®]) Health Professional Version. National Cancer Institute. Available at: <http://www.cancer.gov/cancertopics/pdq/supportivecare/pain/HealthProfessional>
25. Deandrea S, Montanari M, Moja L, Apolone G. Prevalence of undertreatment in cancer pain. A review of published literature. *Ann Oncol*. 2008;19:1985-91. Epub 2008 Jul 15.
26. Rinaldi RC, Steindler EM, Wilford BB, Goodwin D. Clarification and standardization of substance abuse terminology. *JAMA*. 1988;259:555-557.
27. Miaskowski C. The use of risk-management approaches to protect patients with cancer-related pain and their healthcare providers. *Oncol Nurs Forum*. 2008;35 Suppl:20-4.
28. Passik SD, Kirsh KL. The interface between pain and drug abuse and the evolution of strategies to optimize pain management while minimizing drug abuse. *Exp Clin Psychopharmacol*. 2008;16:400-4.
29. U.S. Food and Drug Administration Center for Drug Evaluation and Research. Questions and answers on the *Federal Register* Notice on drugs and biological products deemed to have Risk

Evaluation and Mitigation Strategies. March 27, 2008. Available at:
http://www.fda.gov/CDER/regulatory/FDAAA/FR_QA.htm