Managing Breakthrough Pain: A Clinical Review With Three Case Studies Using Oral Transmucosal Fentanyl Citrate

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Patients with cancer often experience pain. Pain can be related to cancer treatment (surgery, chemotherapy, or radiation therapy), to a tumor itself, or to an unrelated etiology. Patients often experience more than one type of pain, which requires integrating multiple treatment modalities into their plans of care. In patients reporting moderate to severe pain, two components of pain usually are present: persistent pain and breakthrough pain (Portenoy & Hagen, 1989, 1990). Because persistent pain and breakthrough pain are distinct entities that should be addressed individually, correctly assessing pain and developing appropriate pain management plans are challenging.

One patient’s description of her pain serves as an example of the two distinct components of chronic pain. She stated, “[My] pain is deep and constant, but throughout the day, there is a pain that comes on without warning, and it takes my breath away.”

Pain management begins with screening for pain using a numeric, verbal, or visual analog scale that is appropriate for the age, cultural background, and cognitive functioning of the patient. Once the presence of pain is established, a thorough assessment is conducted to determine the etiology and pathophysiologic basis of the pain. The assessment includes a neurologic and musculoskeletal physical examination, the determination of any comorbid conditions, and a medication history. Clinicians often use the OLD CART acronym (onset, location, duration, characteristics, aggravating factors, relieving factors, and temporal relationship) to assess the type of pain (see Figure 1). Screening for distress also is a crucial component of pain assessment. Distress, regardless of its origin (physical, emotional, or spiritual), affects how a patient rates physical pain intensity.

The presence and severity of persistent and breakthrough pain drive the plan of care and the types of medications that are prescribed. Breakthrough pain generally is not well understood by clinicians; therefore, it often is not managed adequately. Knowing how to assess and manage it helps to create successful pain management plans. Through the use of case studies and discussion, this article addresses the characteristics of and provides management strategies for breakthrough pain.

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**Persistent Pain**

Persistent pain is defined as pain experienced for longer than 12 hours per day. It also is known as constant, baseline, or basal pain. According to pain management experts, moderate to severe persistent pain should be treated with opioids (see Figure 2), using an oral or transdermal route of medication when possible (Agency for Health Care Policy and Research, 1994; World Health Organization, 1990).

Persistent pain is best treated with around-the-clock (ATC) dosing of pain medications to provide a steady, therapeutic level of medication in a patient's blood and to limit side effects that can occur with as-needed (PRN) dosing. Because opioids have proven to be effective for most cancer pain and chronic nonmalignant pain, they have become the cornerstone treatment for moderate to severe persistent pain. The goal of opioid therapy is to achieve the best possible pain relief while avoiding as many side effects as possible. If side effects are not well controlled, patients may not adhere to recommended treatment plans, and titration of medication to optimal benefit may be difficult.

Sustained-release and long-acting opioid preparations often are used for ATC coverage. Examples of oral sustained-release analgesics include morphine sulfate extended-release capsules (Avinza®, Ligand Pharmaceuticals Inc., San Diego, CA), morphine sulfate controlled-release tablets (MS Contin®, Purdue Pharma, Stamford, CT; Kadian®, Alpharma, Fort Lee, NJ), and oxycodone hydrochloride controlled release (OxyContin®, Purdue Pharma). Fentanyl in a transdermal patch (Duragesic®, Janssen Pharmaceutica, Titusville, NJ) also can be used for ATC coverage. Patients may adhere to treatment plans with these medications because of their sustained-release formulations, which require less frequent dosing intervals. Methadone hydrochloride (Dolophine®, Roxane Laboratories, Columbus, OH), a long-acting lipophilic opioid, may be an alternative treatment for moderate to severe persistent pain and neuropathic pain. Because of its long duration of action, this medication can be taken every six to eight hours. However, methadone is eliminated biphasically and has a long, unpredictable half-life; thus, it must be titrated cautiously. Use of this medication requires knowledge of its pharmacology and experience, and it can be extremely unpredictable (idiopathic pain). It also can occur toward the end of the ATC medication dose (end-of-dose failure). Regularly occurring end-of-dose failure seems to be well managed by increasing the ATC medication dose or decreasing the interval between doses (Pappagallo, Dickerson, & Hulka, 2000).

Assessment of breakthrough pain includes gathering information on the severity, location, duration, precipitating factors, and relationship to the ATC medication dose. Inferred pathophysiology and etiology of the pain syndrome also should be addressed (Portenoy, 1997a, 1997b). In the past, clinicians have managed breakthrough pain episodes by increasing ATC medication doses, even when a patient’s persistent pain already is well controlled; however, this approach often increases side effects, especially sedation, which limits a patient’s physical or mental activity or function (Simmonds, 1999) (see Figure 4). The goal of treating breakthrough pain is to provide relief during the entire episode without overmedicating the patient. Ideally, medication for breakthrough pain should take effect quickly, adequately cover the pain episode, and be short in duration, thus allowing the patient to rapidly gain control of pain to avoid a pain gap, the difference in time between the start of pain and the arrival of meaningful relief (Rhiner & Coluzzi, 1998) (see Figures 5 and 6).

The following three case studies describe practical strategies for effectively managing breakthrough pain.

### Persistent Pain Assessment

**OLD CART:**
- Onset of pain
- Location(s) of pain
- Duration of pain (constant versus intermittent)
- Characteristics (e.g., sharp, dull, throbbing, electric, pins and needles)
- Aggravating factors (e.g., walking, sitting, lying down)
- Relieving factors (e.g., medication, warm shower, positioning)
- Temporal relationship (time of day or night that pain is worse or better)

**FIGURE 1. OLD CART ASSESSMENT**

### Three-Step Analgesic Ladder

**Choice of Agent: Three-Step Analgesic Ladder**

<table>
<thead>
<tr>
<th>Pain rating 7–10</th>
<th>Moderate to severe 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid ± Adjuvant ± Nonopioid</td>
<td></td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Pain rating 4–6</th>
<th>Mild to moderate 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid often with nonopioid ± Adjuvant</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain rating 1–3</th>
<th>Mild 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonopioid ± Adjuvant</td>
<td></td>
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**FIGURE 2. WORLD HEALTH ORGANIZATION ANALGESIC LADDER®**

*Note. Based on information from World Health Organization, 1990.*

**Breakthrough Pain**

Pain is not a static event, and patients often report episodes of breakthrough pain despite taking ATC opioids. Portenoy and Hagen (1989, 1990) found that breakthrough pain occurs suddenly on a background of controlled persistent pain, frequently reaches maximum intensity in three minutes, is moderate to severe in intensity, lasts an average of 30 minutes, and occurs one to four times a day (see Figure 3). Breakthrough pain occurs in 52%–67% (Caraceni & Portenoy, 1999) of patients with cancer who report that their persistent pain is predominantly well controlled with sustained-release opioids. A study of hospice patients indicated a higher prevalence of breakthrough pain, reporting episodes in 86% of patients (Fine & Busch, 1998).

Breakthrough pain can be triggered by various activities (incident pain) or can be entirely unpredictable (idiopathic pain). It also can occur toward the end of the ATC medication dose (end-of-dose failure). Regularly occurring end-of-dose failure seems to be well managed by increasing the ATC medication dose or decreasing the interval between doses. Breakthrough pain episodes by increasing ATC medication doses, even when a patient’s persistent pain already is well controlled; however, this approach often increases side effects, especially sedation, which limits a patient’s physical or mental activity or function (Simmonds, 1999) (see Figure 4). The goal of treating breakthrough pain is to provide relief during the entire episode without overmedicating the patient. Ideally, medication for breakthrough pain should take effect quickly, adequately cover the pain episode, and be short in duration, thus allowing the patient to rapidly gain control of pain to avoid a pain gap, the difference in time between the start of pain and the arrival of meaningful relief (Rhiner & Coluzzi, 1998) (see Figures 5 and 6).

The following three case studies describe practical strategies for effectively managing breakthrough pain.
**Case Study 1**

**Patient History and Characteristics**

Patient 1 was a 47-year-old man with metastatic adenocarcinoma of unknown origin that had metastasized to the T7 vertebra. He was treated with radiation therapy and subsequent resection of the T7 vertebra, bone graft, and stabilization of the spine. After surgery, the patient was troubled by back pain. Magnetic resonance imaging showed a displacement of the hardware because of bone graft failure. The patient’s pain was confined to the thoracic spine and included intercostal neuralgia and radiculopathy related to the epidural tu-

**Treating Breakthrough Pain**

As seen in Case Study 1, identification of the appropriate treatment for breakthrough pain is essential for optimal pain relief. The medications commonly used for breakthrough pain include morphine, hydromorphone, and oxycodone. Combined opioid and nonopioid medications also are prescribed but are limited in dosing options because of poor efficacy and safety concerns. Morphine, hydromorphone, and oxycodone are hydrophilic opioids that bind with mu receptors. Their onset of action is approximately 30–40 minutes unless they are given via IV, and although they are referred to as short acting, their duration of activity is approximately three to four hours.

If a patient’s persistent pain is generally well controlled for most of the day and a short-acting pain medication is not providing adequate coverage for his or her incident pain, then switching to a more appropriate breakthrough pain medication is suggested. Side-effect profiles of medications also play a role in determining which medications are appropriate to use in treating breakthrough pain. For example, fentanyl has been associated with less severe gastrointestinal side effects (nausea, vomiting, and constipation) than other opioids (Allan et al., 2001; Muijsers & Wagstaff, 2001).

Patient 1 benefited from a novel approach to treating breakthrough pain, an OT delivery system that allows medication to be absorbed through the oral mucosa. The OT delivery form of fentanyl citrate comes in the form of a solid matrix attached to a handle; the matrix is massaged inside the cheek for 15 minutes until it dissolves. This delivery system allows the drug to produce analgesia as quickly as IV morphine because (a) the oral mucosa is 20 times more permeable than the skin and is highly vascular, and (b) fentanyl is lipophilic, or fat soluble, which causes greater absorption and contributes to the medication’s ability to cross the blood-brain...
Case Study 2
Patient History and Characteristics

Patient 2 was a 42-year-old man who was diagnosed with a nonseminomatous germ-cell tumor. He underwent a right inguinal orchietomy and chemotherapy with IV cisplatin, doxorubicin, and cyclophosphamide alternated with vinblastine and bleomycin. He was followed for chronic, painful, bilateral peripheral neuropathy of the lower extremities.

The patient described his pain as “numbness and tingling,” primarily in the feet, that extended up to his knees and was always present but not consistent in intensity. He noted that during the past several months, the pain intensity in his feet had become worse, especially his episodes of breakthrough pain. He scored his pain intensity as a 9 out of 10 at worst and as a 2 or 3 out of 10 at best. The patient used a foot massager to provide additional relief for his feet and lower extremities. When asked to rate on a scale from 0–10 how much the pain interfered with different aspects of his life, he scored the interference with general activity, work, mood, and relationships with others all as a 10 and interference with his enjoyment of life as a 2.

The patient’s pain regimen, which had been established by a previous healthcare provider, consisted of 160 mg of oxycodone hydrochloride controlled release taken every 12 hours and 5 mg oxycodone with 325 mg acetaminophen tablets.

Patient 2 was asked to discontinue his practice of using oxycodone hydrochloride controlled release as a breakthrough medication. Further assessment then was required to determine the average daily intensity of the patient’s persistent pain and his breakthrough pain relief rating when treated with oxycodone and acetaminophen tablets. The persistent pain was well controlled; therefore, no need existed to try other medications commonly used to treat neuropathic pain such as tricyclic antidepressants or anticonvulsants. The oxycodone hydrochloride controlled-release dosage was not altered. The oxycodone and acetaminophen combination, however, was not effective for controlling his breakthrough pain during work activities, so its use was discontinued.

An alternative breakthrough medication was prescribed: 200 mcg of OTFC. Patient 2 was instructed to use the medication before he initiated any activities that usually caused his pain to increase. After two weeks, the patient reported better control of breakthrough pain with a decrease in side effects, including nausea, and he was able to decrease his use of the tetrahydrocannabinols for nausea.

Side-Effect Management

Case Study 2 illustrates the importance of side-effect management. Changing the patient’s medication for breakthrough pain improved his pain control and decreased the side effects. Clinical experience has shown that side effects and responses to opioids vary from patient to patient. However, the most common side effects associated with opioid use are nausea, vomiting, constipation, and sedation. Aggressive side-effect management is necessary, otherwise uncontrolled side effects can become limiting factors in the titration of the medications to optimal pain control. An opiate rotation is an option for reducing side effects and enhancing analgesia (Ahmedzai et al., 1994; Bruera et al., 1994).

Thorough assessment of side effects is essential. An individual who experiences nausea upon initiation of opioid use can be assured that the symptom is time limited and usually can be controlled with an antiemetic. However, a patient who has been using opioids for several weeks and develops nausea or vomiting also should be evaluated for constipation, including a bowel movement history and rectal examination. Patients often underestimate constipation until it is so severe that they experience diarrhea. Diarrhea generally is not seen when opioids are taken ATC; however, mitigating circumstances may exist, such as enteric...
infection that can cause loose, watery stools, which can indicate obstipation. Sedation associated with opioid use can be managed by lowering the opioid dose (if doing so would not compromise comfort), performing an opioid rotation, or adding a stimulant (e.g., methylphenidate), steroid (e.g., dexamethasone), cholinesterase inhibitor (e.g., donepezil), or wakefulness-promoting agent (e.g., modafinil) (Slatkin, Rhiner, & Bolton, 2001). Sometimes adjuvant medications such as anticonvulsants and tricyclic antidepressants can be prescribed to assist with analgesia if side effects from opioids prove to be problematic.

**Case Study 3**

**Patient History and Characteristics**

Patient 3 was an 87-year-old woman with a history of breast cancer in her left breast. She was treated with a lumpectomy, lymph node dissection, and external beam radiation therapy. She was diagnosed with local recurrence and distant metastasis to her hip, skull, and other bones. The patient was referred to palliative care for pain and symptom management. Upon initial assessment, the patient reported that she experienced persistent pain at rest and incident pain when she walked and moved. She described the pain as a severe, dull, sore, and aching one that shot down her legs when she walked. She was diagnosed with somatic and neuropathic pain syndromes. The patient’s pain regimen at her initial visit included one tablet of 5 mg oxycodone with 325 mg acetaminophen PRN by mouth two or three times daily, but she still experienced pain. She experienced mild confusion and sedation with the medication. The pain interfered with her sleep and occurred frequently throughout the day, inhibiting her participation in daily living and social activities. The patient’s goal was to have a pain management regimen that would treat her breakthrough pain so that she could attend her granddaughter’s wedding without being in pain or overly sedated.

Patient 3’s regimen was changed to 10 mg oxycodone hydrochloride controlled release taken by mouth every 12 hours for her persistent pain and 200 mcg of OTFC PRN for breakthrough pain. After the change, she stated that her persistent pain had improved; however, she reported that she continued to experience pain when trying to turn over in bed or ambulate. She used two to three OTFC units during the day. Based on the patient’s report, the clinician increased the oxycodone hydrochloride controlled-release dose to 20 mg taken by mouth every 12 hours and increased the OTFC dose to 400 mcg PRN. At the next visit, the patient reported being able to sleep during the night but said that she was too sedated during the day.

Because she had incident pain associated with movement, the patient was prescribed less basal or ATC medication and larger doses of breakthrough pain medication to help her move comfortably. Her breakthrough pain dose was maintained at 400 mcg of OTFC prior to doing any activity, and the oxycodone hydrochloride controlled-release dose was decreased to 10 mg taken orally in the mornings and 20 mg at night. She reported good control of her persistent pain and complete relief from her breakthrough pain at the follow-up visit. The patient achieved her goal of attending her granddaughter’s wedding and was able to dance with her husband, an activity she had believed that she never would be able to do again.

Patient 3’s disease continued to progress over several years, despite the use of palliative chemotherapy, so she was admitted for hospice care services. At that time, the level of her persistent pain was increasing, so her oncologist titrated her oxycodone hydrochloride controlled release to 30 mg by mouth every 12 hours. No side effects were noted. She was prescribed an adjunct medicine, 750 mg of choline magnesium trisalicylate (Trilisate®, Purdue Pharma) by mouth twice daily, to reduce the inflammatory component of the bone pain. The patient continued to obtain relief from her breakthrough pain with 400 mcg of OTFC PRN; she typically required four to six units per day to maintain her desired level of activity.

Many clinicians are hesitant to prescribe opioids for older patients and instead often use cyclooxygenase 2 inhibitors in this age group. Although less gastric irritation occurs, a risk still exists for renal compromise, which warrants close observation through laboratory monitoring. Opioids can be a safer alternative in older patients.

**Titration of Breakthrough Pain Treatment**

Patient 3’s treatment plan for breakthrough pain demonstrates the significance of individual titration. In the past, the recommended approach for determining the appropriate breakthrough pain dose was one-third of the 12-hour ATC medication or one-sixth of the 24-hour ATC medication dose. This approach was based solely on anecdotal experience (Portenoy, 1997b; Portenoy & Hagen, 1990). However, in Case Study 3, the strength of the patient’s breakthrough pain medication, OTFC, did not require adjustment as the ATC medication was increased to 30 mg of oxycodone hydrochloride controlled release taken every 12 hours, which illustrates that, in this case, no correlation existed between the ATC medication dose and the strength of the OTFC unit. Each must be adjusted to the patient’s analgesic needs. This clinical observation is supported by findings from various studies, including research on OTFC and oral immediate release morphine (Christie et al., 1998; Portenoy et al., 1999). The correct dosage strength is that which best relieves the episode of breakthrough pain and must be determined through individualized titration.

**Summary of Three Case Studies**

This series of case studies demonstrates that breakthrough pain is a unique experience that has physical and emotional components. Comprehensive and systematic assessment and management must be achieved to properly address the total pain experience. Pain management begins with an understanding of persistent and breakthrough pain to determine the appropriate medications. Breakthrough pain is not well understood and, as a result, often is not managed well; however, if assessment and management of breakthrough pain are integrated into daily nursing practice, adequate pain relief with limited side effects and better quality of life can be provided.

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**References**


For more information on this topic, visit the following Web sites.

**MedlinePlus Drug Information: Fentanyl (Systemic)**

**Cancer Pain Relief: What Is Duragesic?**
[www.cancerpainrelief.com](http://www.cancerpainrelief.com)

Links can be found at [www.ons.org](http://www.ons.org).

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**Rapid Recap**

**Managing Breakthrough Pain: A Clinical Review With Three Case Studies Using Oral Transmucosal Fentanyl Citrate**

- Chronic pain has two components: persistent pain and breakthrough pain.
- Breakthrough pain is not well understood by clinicians and, therefore, often remains inadequately treated.
- Persistent and breakthrough pain require individual, thorough assessment to determine the pathophysiology of each and to ensure the best plan of care.
- Treating breakthrough pain with a medication whose speed and duration of action closely match the onset and duration of episodes of breakthrough pain can help to significantly reduce the pain gap and limit side effects.