Case Studies in Breakthrough Pain

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ABSTRACT

Objective. To illustrate the variable presentations of and treatments for breakthrough pain (BTP).

Design. Five cases of BTP were selected by the author, and treatment options were then considered.

Results. Breakthrough pain presents in many different ways in clinical practice. Clinicians must first evaluate patients to identify the subtype, etiology, severity, and pattern of BTP, and then use that information to suggest appropriate interventions. Whenever possible, correctable causes of BTP should first be addressed. A variety of treatment tools are available, including opioid analgesics, nonopioid analgesics, adjuvant agents, nonpharmacologic strategies, and procedural and surgical interventions. In many cases, more than one treatment option will be appropriate, but in all cases, regular communication between patient and clinician will be needed to achieve optimal control of BTP.

Conclusion. Treatment of BTP should be individualized by using a multidisciplinary approach to address each patient's pain profile.

Key Words. Breakthrough Pain; Opioid Analgesics; Nonopioid Analgesics; Adjuvant Agents; Nonpharmacologic Strategies; Case Studies

Introduction

Breakthrough pain (BTP) has been defined as a transitory flare of pain superimposed on an otherwise stable pain pattern in opioid-treated patients [1], and more broadly as any acute transient pain that flares over baseline [2]. In general, BTP is abrupt in onset—except in the case of end-of-dose analgesia failure, when it may occur more gradually—and is usually intense and transient. BTP episodes can be predicted in end-of-dose failure and some types of incident pain, and effective treatment strategies can usually be developed that minimize the BTP episodes. In contrast, idiopathic and unpredictable incident pain episodes are not precipitated by a readily identifiable cause and are therefore much more difficult to treat (Figure 1). Most of the currently available opioid analgesic compounds do not adequately relieve these types of BTP because they have an onset of action and duration of effect that does not coincide with the onset and duration of the patient's pain (Table 1).

Breakthrough pain should be treated like any other clinical condition: the patient should first be evaluated to determine the subtype, cause, severity, pattern, and location of BTP (Figure 2) [3]. This information provides a working diagnosis and hence identifies appropriate interventions for that patient. When possible, a surgically correctable cause of BTP should be identified and addressed, which may help to minimize the BTP burden for the patient. Treatment examples include radiation therapy for palliation of secondary bone lesions, surgical debulking of solid tumors, and vertebroplasty for previously undiag-
nosed compression fractures [4–6]. Multimodality treatment approaches that may include pharmacologic therapy and various nonpharmacologic interventions, such as physical and psychosocial therapies, are likely to provide the best results [2,7].

Around-the-clock (ATC) drug therapy should be tailored to control chronic pain as well as minimize the potential occurrence of BTP [8]. The dose and/or dosing frequency of the ATC analgesic should be adjusted to not only limit the frequency of BTP, but also maximize the patient’s activity level and level of alertness and cognition. Thus, the clinical challenge is to find a dose or dosing frequency for the ATC medication that minimizes the level of baseline pain and the frequency and intensity of BTP episodes while not significantly impairing the patient’s activity level or cognition. In addition, some predictable causes of BTP can be effectively treated with nonopioid or adjuvant medications, such as antitussives if coughing triggers a BTP episode or laxatives if constipation causes colorectal spasms (Table 2). Treatment of predictable-incident BTP should

![Figure 1](image1.png)  
**Figure 1** Breakthrough pain (BTP) subtypes.

![Figure 2](image2.png)  
**Figure 2** Evaluation and treatment options for breakthrough pain (BTP).

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### Table 1  Commonly used opioid analgesics for the treatment of pain and breakthrough pain

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulations</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>Oral liquid; tablet; parenteral</td>
<td>Moderate to severe pain</td>
</tr>
<tr>
<td>Oxycodone alone and with acetaminophen</td>
<td>Liquid capsule; tablet</td>
<td>Moderate to moderately severe pain</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Parenteral; tablet; oral liquid; suppository</td>
<td>Moderate to severe pain</td>
</tr>
<tr>
<td>Hydrocodone with acetaminophen</td>
<td>Tablet; oral liquid</td>
<td>Moderate to moderately severe pain</td>
</tr>
<tr>
<td>Oral transmucosal fentanyl citrate</td>
<td>Lozenge</td>
<td>Breakthrough cancer pain</td>
</tr>
<tr>
<td>Transdermal fentanyl citrate</td>
<td>Patch</td>
<td>Chronic pain</td>
</tr>
<tr>
<td>Codeine with acetaminophen</td>
<td>Tablet</td>
<td>Mild to moderately severe pain</td>
</tr>
</tbody>
</table>

Compiled from the 2005 Physicians’ Desk Reference, electronic version; not a comprehensive list.
Driver

not depend solely on drug therapy. Behavioral techniques and other nonpharmacologic interventions may be useful in a variety of situations and may help avoid polypharmacy approaches that could prove deleterious to some patients [2,7].

The practical application of these principles is illustrated in the following five cases. As will be apparent in reviewing the cases, there often are several different ways to effectively treat a specific pain problem, and all are reasonable approaches. It is emphasized that the cases are meant to be illustrative of common BTP problems but do not include the actual medical information of specific patients.

Case Studies

Case Study No. 1: Chronic Low Back Pain

A 62-year-old man presented with a 10-year history of lumbar postlaminectomy pain syndrome. He works full-time as a building contractor on commercial projects, but primarily works at a desk. He underwent two lumbar laminectomies 12 and 4 years ago for disk disease, and ever since, he has had chronic back pain and occasional radiating leg pain. He takes a sustained-release opioid twice daily—at 7 AM upon waking and at 7 PM. This provides adequate control of his baseline persistent pain without any adverse effects. He rarely needs any additional medication during the first part of the day. However, in the late afternoon, he often has three to four episodes of moderate-to-severe BTP localized to his back.

What type of BTP does he have? What is the best next step to manage this patient’s BTP?

This patient has “end-of-dose” BTP. His baseline persistent pain appears to be adequately controlled during the first part of the workday, but by mid-afternoon, he does not have adequate analgesia. Nonpharmacologic treatment recommendations should include avoiding sitting in one position for prolonged periods; utilizing “back-smart” precautions, such as bending at the knees and not the back when lifting heavy objects; and doing back exercises, such as William’s stretching exercises for 15 minutes three times a day. The application of portable ice or heat packs to his low back during the drive home can also help.

If these treatment options are ineffective, he might benefit from “asymmetric” dosing of the sustained-release opioid. This approach would involve a higher morning dose while leaving the evening dose the same, though this could lead to daytime sedation. Another option would be switching to a three-time-daily dosing schedule of the sustained-release opioid or adding a lower dose of short-acting opioid in the mid-afternoon.

Case Study No. 2: Cancer-Related Visceral Pain

A 43-year-old woman with advanced ovarian cancer presented with chronic abdominopelvic visceral pain related to carcinomatosis. She is being treated with transdermal fentanyl patches at a dose of 100 µg per hour, and she changes patches every 3 days. After applying a new patch, she has one or two BTP episodes during the first and second days, but three to four episodes on the third day. Her BTP episodes are intense, sporadic, and may occur at various times during the day. There is no physical activity she can associate with their onset. She takes short-acting oral morphine at a dosage of 15 mg at the onset of her BTP episodes, but complains that the medication does not seem to work fast enough and leaves her feeling sleepy for the next several hours.

What is the best way to manage this patient’s BTP?

This patient has end-of-dose-failure BTP and some unpredictable BTP. The first step is to try to adjust the ATC analgesic regimen to better match the patient’s pain profile. One way this can be accomplished is to increase the dosage of transdermal fentanyl that is applied every 3 days. If this approach fails or results in unacceptable adverse events such as sedation, another option would be to maintain the same dose but reduce the dosing interval of the transdermal fentanyl to two rather than 3 days. This is reasonable because the prescribed dosage seems to limit the number of BTP episodes during the first 2 days of each patch application. BTP episodes that occur despite these changes are likely to be unpredictable incident or idiopathic subtypes. The ideal pain reliever for these episodes should therefore have a very rapid onset of action and sufficient analgesic strength.
and duration of effect to match the pattern of severity of the BTP episode, such as oral transmucosal fentanyl citrate.

Case Study No. 3: Tic Douloureux (Trigeminal Neuralgia)
A 65-year-old oral cancer survivor presented with chronic right facial and neck pain that he developed 6 years ago after undergoing cancer treatment with radiation and surgery. Two years ago, he had shingles on the left side of his face, which resulted in left facial postherpetic neuralgia in the distribution of the first and second branches of the trigeminal nerve. He had been obtaining acceptable pain control with gabapentin [9]. Over the past 3 months, he developed BTP characterized as two to three episodes of paroxysmal lancinating pain each day. Each BTP episode strikes suddenly, is debilitating, and persists for 20–30 minutes. The pain may be precipitated by shaving or brushing his teeth, but more often it occurs without any apparent cause.

What is the best next step to manage this patient’s BTP?
Neuropathic pain results from structural changes to the central or peripheral nervous system and may occur spontaneously or in response to specific stimuli [10]. Spontaneous neuropathic pain is typically described as shooting, electric, burning, or cutting in character [3]. In this case, one approach is to switch from gabapentin to another anticonvulsant drug such as carbamazepine [11]. It also is appropriate to consider a surgical intervention, particularly if there is good initial response to the antiepileptic medications. Procedures such as percutaneous gasserian ganglion ablation or microvascular decompression of the proximal trigeminal nerve at the brainstem have led to substantial relief or cure in many patients with trigeminal neuralgia [12–14].

If these approaches fail to reduce the frequency and intensity of BTP episodes, this patient may benefit from a short-acting opioid with a very rapid onset of action and relatively short duration of effect, such as a transmucosal fentanyl product that could be taken at the first sign of BTP.

Case Study No. 4: Vertebral Compression Fractures
An 80-year-old woman who was healthy and active until the last 2–3 years presented for evaluation and treatment when she developed severe back pain that was exacerbated with walking, bending, or lifting. She has a stooped posture that appears to have worsened over the last several months based on reports from family members. A magnetic resonance imaging scan of her spine revealed 80% loss of height of the bodies of the T7 and T8 vertebrae. She has been obtaining some pain relief with daily use of over-the-counter nonsteroidal anti-inflammatory drugs (NSAIDs), but the episodic pain is becoming increasingly debilitating, and she is becoming more depressed as the debilitation increases. Treatment with opioids was not tolerated because it caused severe confusion and somnolence.

What is the best next step to manage this patient’s BTP?
Vertebroplasty and kyphoplasty are minimally invasive procedures that have been shown to effectively restore the normal height of collapsed vertebral bodies and thereby significantly relieve the pain associated with the collapse [4,5]. Physical therapy and a back brace are temporizing measures that may help in the short term, but these are unlikely to provide the long-term pain relief associated with vertebroplasty.

Case Study No. 5: Osteoarthritis with Disabling Knee Pain
A 67-year-old woman presented with painful osteoarthritis in both knees. She was previously treated with NSAIDs but experienced burning epigastric pain not associated with gastrointestinal bleeding as an adverse event associated with those medications. She recently began an opioid regimen consisting of sustained-release morphine 30 mg twice daily, with short-acting morphine 15 mg prescribed every 4 hours as needed for BTP. She has been using the short-acting morphine up to five to six times each day, but is concerned that despite these measures, the pain is increasing.

What is the best next step to manage this patient’s BTP?
Osteoarthritis is a common condition that affects older individuals and is often associated with significant pain and disability. Treatment strategies usually are designed to minimize pain and improve patient function and quality of life [15]. In this case, treatment with sustained-release morphine is not adequately controlling the patient’s baseline persistent pain, as suggested by the need for short-acting morphine five to six times per day. Several treatment options may be appropriate and include increasing the dosage of sustained-release morphine. Due to the frequent use of short-acting morphine, this patient is already receiving a high daily opioid dose. By rais-
ing the sustained-release morphine dosage, it should be possible to achieve a more consistent level of pain control and reduce the need for breakthrough medication. Another reasonable option is to resume NSAID treatment, provided it is given with gastric-acid-reducing therapy. Other options include intra-articular steroid injections, treatment with glucosamine, use of adjuvant medications, opioid rotation, or changing the short-acting opioid formulation.

Summary

These patient cases illustrate a variety of treatment approaches available to address the complex array of pain presentations commonly encountered in clinical practice. Opioids are the mainstay of treatment for BTP, but the opioid regimen needs to be tailored for each patient. Moreover, adjuvant drug therapies, nonpharmacologic strategies, and surgical interventions should be considered on a case-by-case basis. Clinicians should regularly evaluate the patient's response to treatment, particularly after any changes in treatment have been made, and should consider further modifications until good control of BTP is achieved. Because a treatment strategy that is effective for one patient with BTP will not necessarily be effective for other patients—even if they have the same type of BTP—it is important that clinicians take a multidisciplinary approach to individualizing treatment of BTP.

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References