

# Impact and management of breakthrough pain in cancer

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**Current Opinion in Supportive and Palliative Care** 2009, 3:1–6

### Purpose of review

To outline the impact of breakthrough pain, the evidence for the current management and new treatment options that are becoming available.

### Recent findings

Breakthrough pain is a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain. Despite its self-limiting nature, breakthrough pain can place significant physical, psychological, and economic burdens on both patients and their carers. The successful management breakthrough pain may require a combination of pharmacological and nonpharmacological treatment strategies; supplemental analgesia, known as rescue medication, is a common pharmacological treatment option. The ideal rescue medication should have a rapid onset, good efficacy, relatively short duration of action, and minimal adverse effects and is best administered before or soon after breakthrough pain has started. Although oral opioids are commonly used, there is increasing evidence that transmucosal opioids may be more effective.

### Summary

Breakthrough is a common heterogeneous pain state that can have a devastating impact on both patients and carers. Despite the growing literature on breakthrough pain, there are still many aspects yet to be addressed including an urgent need to standardize terminology, for carefully designed epidemiological studies and for well designed controlled trials comparing the different treatment options.

### Keywords

breakthrough pain, cancer, pain, palliative care

Curr Opin Support Palliat Care 3:1–6  
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1751-4258

## Introduction

Pain is regarded as the most feared of cancer symptoms, so effective analgesia is essential to good patient management. Even when background pain is well controlled, many patients may experience brief, self-limiting exacerbations of severe pain known as breakthrough pain, a complex pain state that is increasingly recognized as an important clinical problem. In the past 15 years, there has been increasing interest in breakthrough pain reflected in the increasing number of published studies in the literature which, in turn, has led to debate on a number of issues including definition, assessment and management.

## Defining breakthrough pain

Breakthrough pain is a transient exacerbation of pain that occurs either spontaneously or in relation to a specific predictable or unpredictable trigger despite relatively stable and adequately controlled background pain [1<sup>•</sup>]. The definitions of breakthrough pain have however

varied in the literature. Some investigators have described breakthrough pain only after background pain has been controlled [2] whereas others define it irrespective of analgesic regimen or in patients with uncontrolled background pain who experience exacerbations [3]. This inconsistency was highlighted by an international study that suggested the term breakthrough pain is either defined or recognized differently in different countries [4].

The lack of consensus on a formal definition has led to difficulties when comparing studies and recommending management strategies. Given the importance of distinguishing breakthrough pain from uncontrolled background pain, it has been suggested that three questions would be helpful to distinguish between the two [1<sup>•</sup>] that are as follows:

- (1) Does the patient have background pain?
- (2) Is the background pain adequately controlled?
- (3) Does the patient have transient exacerbations of pain?

If the patient answers 'yes' to all three questions, then they have breakthrough pain.

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### Impact of breakthrough pain

Studies have evaluated the characteristics of breakthrough pain in patients attending cancer centres, pain clinics, hospice in-patient units and hospice outpatients and prevalence varies between 20 and 90% depending on the patient group and definition used [5]. The clinical features of breakthrough pain vary from individual to individual and may vary within an individual over time [6]. Nevertheless, breakthrough pain is generally related to background pain [2,7,8], frequent in occurrence (approximately four episodes daily) [2,7,8,9], acute in onset (reaching maximum severity within 5 min) [7,9], short in duration (most subsiding within 30 min) [2,8,9] and severe in intensity [2,7,8,9].

Two subtypes of breakthrough pain exist and may exist as multiple pains in an individual patient [2,7,8,9].

- (1) Incident pain, reported in 32–94% of patients [10,11], may be predictable when precipitated by volitional factors (e.g. movement) or unpredictable when precipitated by nonvolitional factors (e.g. bladder spasm). Incident pain has been shown to be a poor predictor of successful pharmacological therapy [11,12].
- (2) Spontaneous pain has been reported in 28–45% of patients [2,10]. It develops in the absence of a specific trigger and can occur randomly and unpredictably with little or no warning, making management difficult.

End-of-dose pain, which consistently occurs just prior to the next scheduled dose of around-the-clock analgesia, because of an inadequate analgesic dose or too lengthy administration interval, is not a breakthrough pain subtype as baseline pain is (by definition) not controlled with the optimum dose of around-the-clock medication.

Despite the self-limiting nature of breakthrough pain, it can place significant physical, psychological, and economic burdens on both patients and their carers. Patients with breakthrough pain are often less satisfied with their analgesic therapy [7,8], they have decreased functioning because of their pain and may also experience social and psychosocial consequences, such as increased levels of anxiety and depression [7]. Breakthrough pain can be a poor prognostic indicator [11,13], and the site of breakthrough pain may predict the response to treatment [9]. Furthermore, inadequately relieved breakthrough pain can place additional burdens on the healthcare system (e.g. increases in emergency and medical visits, more hospital admissions, and longer stays) [14] and on patients

with increased direct costs (e.g. prescriptions) and indirect costs (e.g. child care) [15].

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### Management of breakthrough pain

The aim of breakthrough pain management is to reduce the intensity, severity, and impact of each pain. There is no gold standard treatment for the management of breakthrough pain, but, given the heterogeneous nature of the pain, successful management is likely to be best achieved by a thorough assessment, good communication, reassurance about pain relief, and encouraging patient and carer participation. Furthermore, treatment should be integrated into the overall care regime; it should be appropriate for the stage of the disease and may involve both pharmacological and nonpharmacological treatment modalities.

Management involves a number of steps including

- (1) general assessment (e.g. pain assessment, explanation);
- (2) lifestyle changes (e.g. coping strategies);
- (3) management of reversible causes (e.g. incident pain precipitants);
- (4) modification of the pathological processes (e.g. anti-neoplastic therapies);
- (5) symptomatic management of breakthrough pain (e.g. pharmacological and nonpharmacological);
- (6) reassessment (e.g. evaluation of pain and management).

### Assessment of breakthrough pain

No validated tool for the clinical assessment of breakthrough pain currently exists though breakthrough pain is usually characterized according to its location, severity, temporal characteristics, relationship to regular analgesia, precipitating factors, predictability, pathophysiology, aetiology and palliative factors [1\*]. It is important to differentiate breakthrough from background pain and, in particular, uncontrolled background pain; in most cases, background and breakthrough pain will be related [2,8,9]. Inadequate assessment may lead to the utilization of ineffective or inappropriate treatment or both.

### Lifestyle changes

Specific interventions that encourage lifestyle changes are relatively inexpensive that can empower patients to accept responsibility for their own pain management and be more involved in their treatment. For example, patients may be taught pacing to reduce activities that precipitate breakthrough pain when they are most likely to occur. They may be encouraged to use specific aides for activities of daily living (e.g. washing, dressing and cooking), to engage in specific exercises, or to use the help provided by family in a way that maximizes benefit.

### Management of reversible causes

Breakthrough pains may be precipitated by numerous processes, some of which are amenable to either pharmacological or nonpharmacological therapy. Pain related to cough or constipation, for example, may be effectively ameliorated by an antitussive or laxative, respectively. In contrast, pain related to joint movement may be addressed in some cases by appliances that limit the mobility of the joint.

### Modification of the pathological processes

Interventions that modify pathological processes may result in an improvement in both background and breakthrough pain. These interventions include chemotherapy, radiation therapy, and surgery and can be either single or in combination. Relief of breakthrough pain is likely to occur only when the response to these therapies is substantial; however, it should be noted that while there is good evidence for the efficacy in managing background pain, there is relatively little evidence for the management of breakthrough pain.

### Nonpharmacological symptomatic treatment

A variety of nonpharmacological methods have been described by patients as being helpful and include rubbing/massage, application of heat, application of cold, distraction techniques and relaxation techniques [1<sup>•</sup>]. These nonpharmacological strategies can be tried either before, or alongside, pharmacological therapy. Although patients often volunteer that such treatments are helpful, there is relatively little evidence to support the use of these interventions in the treatment of breakthrough pain episodes.

### Pharmacological symptomatic treatment: around-the-clock analgesia

#### *Nonopioids*

Optimizing the around-the-clock analgesia according to the principles of the World Health Organisation analgesic ladder [16] may help ameliorate breakthrough pain; both nonopioid or adjuvant analgesics should be considered though there is limited evidence for the efficacy. For example, though paracetamol is widely used in the management of mild cancer pain, the evidence for its efficacy is from studies in acute postoperative pain [17]. Furthermore, though the evidence for nonsteroidal anti-inflammatory drugs (NSAIDs) suggests they are effective in background pain [18], there is no specific evidence in breakthrough pain.

Adjuvant analgesics should be considered at all stages of the patient's illness and at each step of the WHO analgesic ladder and commonly used for neuropathic pain, which can present with a component of breakthrough pain. Paroxysmal neuropathic pains can be among the most challenging breakthrough pains, and

the addition of one or more drugs specific for neuropathic pain may help reduce or prevent them [19,20]. Patients with metastatic bone pain, raised intracranial pressure, obstruction of hollow viscus, and organ infiltration may also benefit from adjuvant analgesics.

#### *Opioids*

Traditionally, opioids have played an important role in the management of breakthrough pain. Integral to the assessment process, therefore, is an assessment of the degree of opioid responsiveness of the presenting breakthrough pain, which may be influenced by several factors related to the pain, the patient, or the opioid.

In the absence of treatment-limiting side effects, an increase in the around-the-clock opioid dose may be considered in an effort to reduce the frequency or intensity of breakthrough pains. In a study of patients presenting to a haematology/oncology service with mixed breakthrough pains, an increase in around-the-clock medication improved both background and breakthrough pain [9]. Another study of patients with incident breakthrough pain also showed improvement following increases in around-the-clock analgesia [21]. Although there is some evidence for this strategy, it is difficult to draw conclusions as the studies are few, involve small numbers of patients, explore different pain states, and use different outcome measures. Nonetheless, optimizing around-the-clock opioid dose for breakthrough pain could be attempted, and the dose then lowered again if the patient experiences adverse effects between episodes of breakthrough pain.

### Pharmacological symptomatic treatment: rescue analgesia

The use of supplemental doses of analgesics (also known as rescue medication) is the most common pharmacological treatment strategy for managing breakthrough pain. Given the aforementioned characteristics of breakthrough pain, the ideal rescue medication should be efficacious, patient friendly, with a rapid onset of action, a relatively short duration of action, and minimal adverse effects and can be used either prophylactically for predictable pains or as soon as pain starts for unpredictable pains.

#### *Nonopioids*

Both nonopioid analgesics and adjuvant analgesics are commonly used as rescue medication. However, the slow onset, relatively long duration of action, and dose-limiting adverse effects of nonopioids often limit their utility. A number of reports have described the use of other adjuvant analgesics in the management of breakthrough pain, including nitrous oxide, ketamine, and midazolam [22–24]. The evidence for these treatments is mostly in the form of case reports or small controlled studies and is often conflicting.

*Oral opioids*

The most common method of providing rescue medication is with normal-release oral formulations of morphine, hydromorphone, or oxycodone. In most cases, oral opioids can take 30–40 min to produce an analgesic effect, reach a peak at one hour and last for 4 h [25]; therefore, breakthrough pain with a slow onset and lasting for more than one hour is likely to respond best to oral opioids, whereas breakthrough pain of short duration (i.e. the majority) may not. There is some evidence to suggest that methadone has a faster onset of action than the other oral opioids [26]; however, its use is complicated by complex pharmacokinetics and pharmacodynamics.

The most effective dose of rescue medication also remains unknown. A fixed proportion of the around-the-clock medication is usually advised, typically 10–15% of the daily dose [27], though this is based on anecdotal evidence only. As breakthrough pain can vary in causes, intensity, and duration, it may be possible that the effective rescue dose will also vary. Indeed, it has been recommended that the starting dose should be reviewed, and adjusted if necessary, according to the beneficial and adverse effects reported by the patient [1•].

Although the oral route is often preferred for rescue medication, the typical characteristics of breakthrough pain, particularly the fact that the pain peaks within minutes, suggest that responsiveness to an oral drug may be less than optimal because the onset of analgesia may follow the peak of the target pain. Patients may, therefore, obtain very little or delayed relief, even when rescue medication is used prophylactically, or adverse effects may become problematic due to effects of the medication that persist long after the pain has resolved.

It has been suggested that altering the formulation of rescue medication may improve efficacy. In an open study of patients with cancer background and breakthrough pain switched to an effervescent formulation of morphine, significantly more pain reduction and greater global satisfaction compared with their previous oral rescue medication were reported [28]. Other efforts to deliver rescue medication more effectively have explored alternatives to the oral route including parenteral, rectal, inhaled, intranasal, sublingual, and oral transmucosal preparations.

*Parenteral opioids*

Intravenous morphine has been shown to be effective, well tolerated, and safe for the inpatient management of breakthrough pain [29,30], and hydromorphone has been delivered subcutaneously using a ‘pain pen’ [31]. In all three studies, the successful rescue medication was a fixed ration of around the clock opioid. The use of parenteral opioids is not always practical as they are

invasive, inconvenient, and uncomfortable; however, if pain is severe this route appears to be acceptable [32].

*Rectal opioids*

Rectal administration can be useful to patients who are unable to tolerate oral medication or in cases in which the parenteral route is compromised by bleeding disorders or generalized oedema [33]. Several opioids may be formulated as rectal preparations, though availability may vary from one country to another, as may patient and caregiver acceptance. The dose administered is usually the same as the oral dose. Although rectal administration can provide quick pain relief, absorption is variable and so potentially is the amount of pain relief [34].

*Inhaled opioids*

The lungs present a large surface area for drug absorption, and the use of inhaled opioids for postoperative pain has been described [35], but there are few data on patients with breakthrough pain [36]. Although generally acceptable, some patients find nebulizers cumbersome, noisy, and time consuming; furthermore, it is an inefficient way of delivering medication. More precise devices are in development.

*Intranasal opioids*

There are a number of reports describing the nasal administration of opioids [37]. This route allows self-administration of opioid with rapid onset of action, and nasal sprays containing a variety of opioids have been reported [38,39]. A major disadvantage with the currently available opioid preparations is the relatively small volume of drug the nose is able to accommodate; however, more concentrated preparations are currently in development.

*Sublingual opioids*

Sublingual administration leads to rapid absorption and is convenient, accessible, and generally well accepted. Buprenorphine has been available by this route for many years, but its slow rate of onset and long duration of analgesia are not ideally suited to the management of breakthrough pain. A new fast dissolving sublingual fentanyl preparation is now available specifically with design developed for the management of breakthrough pain. The tablet disintegrates into ordered units of carriers adhering to the sublingual mucosa allowing fentanyl to rapidly and effectively permeate the sublingual mucosa and enter the bloodstream [40].

*Oral transmucosal opioids*

Two products are currently licensed by this route. Oral transmucosal fentanyl citrate (OTFC) is a fentanyl-impregnated lozenge, developed specifically for the management of breakthrough pain [41]. OTFC is rapidly absorbed through the oral mucosa and is ideally suited

for breakthrough pain with a rapid onset and short duration. A number of trials have confirmed the efficacy, safety, and tolerability of OTFC; these studies also suggest the successful dose of OTFC cannot be predicted from the ATC opioid dose [42]. The current recommendation, therefore, is that each patient is titrated to a successful dose that produces adequate analgesia and minimal adverse effects.

The second product with marketing authorization in Europe and America is the fentanyl buccal tablet (FBT) [43]. This tablet provides rapid penetration of fentanyl through the buccal mucosa by using effervescence to cause pH shifts that enhance the rate and extent of fentanyl absorption. Compared with OTFC, the buccal tablet provides a larger proportion of the dose transmucosally (48 vs. 22%) and has an earlier  $T_{\max}$  (47 min vs. 91 min). The efficacy of this formulation has been shown in placebo-controlled studies [44] that have demonstrated an onset of effect more rapid than would be expected from oral therapy. As with OTFC, the successful dose of FBT did not correspond to the around-the-clock dose.

## Conclusion

The successful management of cancer pain depends on a comprehensive assessment which must take into account both background and breakthrough pain. As breakthrough pain is a heterogeneous phenomenon that can vary in frequency, intensity, rate of onset, duration, and predictability, a comprehensive assessment is required. The subsequent management plan may require a combination of treatment strategies, including opioids which traditionally have played an important role in the breakthrough pain management. In some cases, optimizing around-the-clock opioids may be helpful; however, the most common strategy is to deliver rescue medication either prophylactically for predictable pains or as soon as pain starts for unpredictable pains. Although oral opioids are commonly used, there is increasing evidence that transmucosal opioids may be more effective.

## References and recommended reading

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- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 79).

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