Breakthrough Pain in Cancer Patients: Characteristics, Prevalence, and Treatment

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“Breakthrough pain” is a common clinical term that has not been conclusively defined or described. Breakthrough pain is a transitory flare of pain experienced when baseline pain has been reduced to a mild or moderate level.

Introduction

Breakthrough pain is currently recognized as an important clinical phenomenon. It is referred to with increasing frequency in the cancer pain literature despite a lack of consensus on a formal definition and despite limited data from controlled research. Contemporary guidelines for the management of cancer pain uniformly recommend the provision of supplemental "rescue" or "escape" doses of short-acting analgesics to manage breakthrough pain, and most recommend monitoring the frequency of breakthrough pain as a gauge of the adequacy of treatment with regularly scheduled analgesics.[1-4] In addition, Bruera and others cite the presence of incident pain, a specific type of breakthrough pain, as one of the few indicators that reliably predict a poor response to treatment with routine pharmacotherapy.[5-8]

Widespread acceptance of empiric treatment and emerging evidence of the utility of breakthrough pain as a prognostic marker demonstrate the importance of breakthrough pain as a key component of cancer pain. Unfortunately, data on breakthrough pain are limited and remain difficult to interpret, presumably due to variations in how the phenomenon is defined, assessed, and treated. Although breakthrough pain occurs in conjunction with baseline pain that is under stable control, the criteria for what constitutes controlled baseline pain vary from investigator to investigator. In addition, investigators differ in their working definitions of breakthrough pain and its subsets, and a number of studies measure only specific types of breakthrough pain. All of these factors contribute to the widely disparate published figures for breakthrough pain prevalence, which range from 19%[9] to 93%.[10]

The clinical significance of breakthrough pain is also controversial. Studies intended to evaluate the adequacy of long-acting analgesics often utilize the incidence of breakthrough pain as a surrogate outcome measure, and imply that the presence of even modest breakthrough pain reflects an inappropriately low dosage of regularly scheduled, around-the-clock (ATC) analgesics.[11-12] Investigators who are concerned with the identification of factors that predict the success or failure of pain therapy associate breakthrough pain with intractability.[5] Still others recommend titration of scheduled and prn (pro re nata, or as needed) analgesics to balance the adequacy of overall and breakthrough pain relief against the intensity of associated side effects and functional impairment.[1,13]

Treatment recommendations for patients with breakthrough pain also vary considerably. All treatment regimens are empiric, and usually involve estimating the dose of breakthrough pain medication as a proportion of the scheduled ATC dosage. Some authorities recommend the use of prn doses equivalent to a scheduled dose at specific intervals.[1,14] Others provide breakthrough pain medication doses every 1 to 2 hours in a dose that is a proportion (usually 5% to 15%) of the total daily scheduled dose.[15]

Rather than being just an artifact of ATC dosing, breakthrough pain appears to represent a distinct heterogeneous clinical entity that warrants careful assessment and an individualized management approach. With the recognition that breakthrough pain comprises a key component of chronic cancer pain, it has become increasingly apparent that there is a critical need for standardization of terminology, carefully designed epidemiologic studies, and controlled trials of various treatment approaches.

Temporal Characteristics of Pain
Various schemata for characterizing cancer pain have been advanced that, when applied, may aid in
diagnosis and the determination of initial and subsequent therapies. These include classifications
based on pain chronicity, intensity, pathophysiology, syndromal presentation, disease stage, patient
characteristics, and temporal features (Table 1). An appreciation of the temporal characteristics of
pain, including the presence and nature of breakthrough pain, is a fundamental requisite to a better
understanding of the pain syndrome and the institution of effective treatment.

The temporal characteristics of pain consist of: (1) the presence or absence of pain at a given
moment in time; (2) its intensity or severity at a given moment in time; and (3) the rate and pattern
of change in intensity or severity over short or long intervals of time (ie, its tempo). Both acute and
chronic pain consist of a series of related events that can be broadly classified as constant or
intermittent. Chronic pain is usually a relatively constant phenomenon punctuated by intermittent
exacerbations. The constant, unrelenting component of chronic pain has been variously referred to
as baseline or basal pain. Superimposed intermittent exacerbations of pain (changes in tempo from
baseline) have come to be known generically as breakthrough pain and have recently become a
focus of intense clinical interest.

The International Association for the Study of Pain (IASP) has established a taxonomy for painful
disorders, which uses an alphanumeric coding system aimed at assisting clinicians and investigators
in comprehensively classifying painful disorders.[16,17] This system classified pain along the
following five axes: region, system, temporal characteristics, intensity, and etiology. Although the
temporal classifications suggested by the IASP may have important implications for researchers,
they are expansive and unwieldy for the clinician managing cancer pain.

### Defining Breakthrough Pain

First, breakthrough pain needs to be distinguished from poorly controlled baseline pain, the pain
emergency, and "crescendo pain." The main feature that distinguishes breakthrough pain from these
other conditions is that, when breakthrough pain occurs, baseline (basal) pain is, by definition, under
relatively stable control.

Although ill-defined and heterogeneous, the pain emergency is best viewed as an acute condition of
mounting pain that occurs either de novo or in the context of a history of well-controlled pain.[18,19]
In contrast to breakthrough pain, for which the cause is usually known and symptomatic treatment
can thus be implemented, a pain emergency mandates a diagnostic evaluation aimed at identifying
the etiology of the pain. Pinpointing the cause of the pain may suggest an appropriate treatment
strategy to limit morbidity and even mortality. Examples of pain emergencies include pain due to
bowel obstruction, pathologic fractures, and epidural spinal cord compression.

Crescendo pain[20] is probably best regarded as a subacute pain emergency characterized by
progressive, unrelenting increases in pain severity. It is usually described in the context of a history
of stable pain due to cancer and has been reported most often in dying patients. The presence of
crescendo pain implies the need to treat mounting basal pain, usually with rapidly titrated doses of
parenteral opioids administered by continuous infusion and supplemental nurse- or
patient-administered boluses.

In contrast to breakthrough pain, treatment of crescendo pain is directed at the entirety of the pain
experience, rather than the exacerbations. Crescendo pain in a dying patient is associated with
special management considerations that may include the use of various alternate routes, anesthetic
or neurosurgical interventions, and even terminal sedation.[20]

Portenoy and Hagen were the first investigators to propose a standardized definition of breakthrough
pain. They defined breakthrough pain as a transitory increase in pain to greater than moderate
intensity occurring on a baseline of pain of moderate intensity or less.[21] Using this definition,
Portenoy and Hagen characterized breakthrough pain in a group of 63 patients. Prior to this seminal
observational study, breakthrough pain had usually been described only as a secondary outcome
measure.[6-10,22,23] Portenoy and Hagen also identified six characteristics that are relevant to
understanding breakthrough pain: the relationship of breakthrough pain to a fixed opioid dose,
temporal characteristics, precipitating events, predictability, pathophysiology, and etiology (Table 2).

### Relationship to Fixed Opioid Dose

Chronic cancer pain is typically composed of variable components of basal pain and breakthrough
pain and, in this respect, differs from acute cancer pain syndromes, such as postoperative and
procedure-related pain, which have more predictable, unidimensional temporal courses.[24] Most
guidelines recommend that chronic cancer pain warranting the use of opioid analgesics be treated
with the concomitant use of two pharmacokinetically distinct preparations of opioid analgesics. Once pain is stabilized (usually with short-acting opioids), baseline pain is typically treated with a relatively long-acting agent, such as oral controlled-release morphine, oral controlled-release oxycodone, or transdermal fentanyl (Duragesic), prescribed on a time-contingent or ATC basis. A short-acting agent with a relatively rapid onset (e.g., immediate-release morphine, hydromorphone, and oxycodone) is prescribed on a symptom-contingent or prn basis. In this context, the frequency with which prn doses are required is used to gauge the need to adjust the dose of basal analgesics.

**End-of-Dose Failure**—Breakthrough pain that bears a consistent relationship to the ATC dosing regimen usually occurs with greater frequency near the end of a dosing interval and is referred to as end-of-dose failure. This form of breakthrough pain typically has a relatively gradual onset and generally lasts longer than pain that is unrelated to the dosing interval.[25] The incidence and severity of end-of-dose failure usually correlate with the adequacy of ATC dosing regimens prescribed for the management of basal pain. End-of-dose failure is typically more prevalent and more severe when either basal (ATC) analgesics are prescribed in inadequate doses or the interval between administrations is excessive. In contrast to other types of breakthrough pain, end-of-dose failure is best managed by modifying the dose or schedule of long-acting ATC opioids.[25]

**Other types of breakthrough pain** include incident pain (sometimes referred to as precipitated pain or movement-related pain) and so-called spontaneous or idiopathic breakthrough pain. Incident pain has a relatively consistent temporal relationship to specific events or activities. Breakthrough pain that is unrelated to either activity or scheduled doses of analgesics is typically referred to as either spontaneous or idiopathic breakthrough pain. It is worth noting that McQuay and Jadad advocate an alternate classification from the one presented here; this system regards breakthrough pain as a subset of incident pain, rather than the reverse.[26]

**Temporal Characteristics: Onset and Duration**
Breakthrough pain can be characterized by its specific temporal features; these include its rapidity of onset, duration, and frequency. The onset of breakthrough pain has been classified as sudden or paroxysmal vs gradual. Sudden or paroxysmal episodes have been arbitrarily defined as those arising within 3 minutes, while gradual-onset breakthrough pain establishes itself more slowly. With regard to duration, an arbitrary value of 20 minutes has been suggested as the cut-off for classifying an episode of breakthrough pain as brief or sustained. Exacerbations of pain that occur very frequently and/or for sustained intervals are probably best regarded as representing a recrudescence of basal pain, rather than breakthrough pain. Studies to date demonstrate considerable variability in the frequency of breakthrough pain, supporting the notion that breakthrough pain is a highly heterogeneous phenomenon.

**Precipitating Events**
As noted, breakthrough pain may be either spontaneous or precipitated by a recognizable event (incident pain or precipitated pain). Precipitated pain may be volitional (i.e., induced by an action subject to some control, such as movement, swallowing, and coughing) or nonvolitional (i.e., caused by events that are subject to less control, such as flatulence, myoclonic jerking, and anxiety). Breakthrough pain associated with volitional activity is commonly referred to as incident pain.

**Predictability**
The concepts of predictable pain and precipitated pain are closely related to that of incident pain, although these terms are not synonymous. Predictable pain refers to the fact that, especially with coaching, patients often are able to correlate the occurrence of breakthrough pain with discrete actions (i.e., precipitating events). Precipitated pains are usually, but not always, predictable. For example, pain related to involuntary movement in patients with myoclonus is precipitated but not always predictable. Seemingly spontaneous pain is sometimes predictable, especially when associated with environmental cues, such as the presence of a family member. When trained to appreciate environmental cues (e.g., stress), patients often can be taught to predict episodes of breakthrough pain with some reliability.[25]

**Pathophysiology**
A pathophysiologic classification of pain that distinguishes among somatic nociceptive, visceral nociceptive, and neuropathic pain is widely accepted and is clinically relevant to breakthrough pain.[27]

**Somatic and Visceral Nociceptive Pain**—Pain of somatic nociceptive origin emanates from injury to nonneurologic, nonvisceral connective tissues, such as muscle, bone, skin, ligaments, and joints. It is characteristically described by patients in familiar terms that are culturally linked to pain, such as
sharp, stabbing, dull, and achy. Prototypical examples of somatic nociceptive pain include soft-tissue trauma, postoperative pain, bone metastases, and pathologic fractures. Pain of visceral nociceptive origin emanates from injury to hollow or solid viscera, is often diffuse, and is characteristically described as vague, dull, dragging, or pressure-like. Examples include labor pain, bowel obstruction, and pain due to liver capsule distention. Somatic and visceral nociceptive pain originate with activation of peripheral A-delta and C nociceptors by noxious mechanical, chemical, or thermal stimuli. Impulses are conveyed along classically described neuroanatomic pain-conducting pathways that include the dorsal horn of the spinal cord, contralateral spinothalamic tract, thalamus, and subcortical and cortical structures. Impulses are modulated by both biochemical and cognitive mechanisms. Somatic or visceral nociceptive pain typically responds robustly and in a relatively linear manner to treatment with opioid analgesics.

Neuropathic pain follows obvious or subclinical injury to parts of the peripheral or central nervous system. It is often, but not invariably, associated with abnormal neurologic findings, ranging from reproducible sensory or motor deficits to subjectively abnormal (dysesthetic) sensations. These abnormal sensations may include paresthesias, hyperalgesia, hyperpathia, allodynia, and hyperesthesia.[17,28,29] In contrast to nociceptive pain, neuropathic pain is often described as a bizarre or foreign experience for which there is no familiar frame of reference. It is typically described in terms that are not culturally linked to pain, such as tingling, numb, burning, lancinating, or shock-like. Prototypical conditions associated with neuropathic pain include diabetic neuropathy, herpes zoster, brachial plexopathy, spinal cord injury, peripheral nerve compression, and amputation. The mechanisms responsible for the development and maintenance of neuropathic pain are less clearly understood than those that contribute to nociceptive pain. They include the propagation of abnormal sensations to the central nervous system, plasticity, and wind-up phenomena. Plasticity is the nervous system’s potential ability to adapt (functionally and structurally) to stimuli, including injury. Wind-up phenomena occur when a barrage of peripheral stimuli acts to facilitate firing of the spinal cord’s wide dynamic range (WDR) neurons, which, in turn, contributes to hyperalgesia. Neuropathic pain may be less responsive to opioids than nociceptive pain, and, in contrast to nociceptive syndromes, is more likely to respond favorably to treatment with adjuvant analgesics (eg, antidepressants, anticonvulsants, and oral local anesthetics).[30] Neuropathic pain has been further categorized as deafferentation or central pain, depending on whether the causative injury involves the peripheral or central nervous system, respectively. This distinction has fallen out of favor, however, based on the perception that it has few practical therapeutic implications.[29]

Etiology
The etiology of breakthrough pain in cancer patients may be related directly to tumor progression (eg, bone metastasis, nerve compression), cancer treatment[31] (eg, postmastectomy pain, osteoradionecrosis, polyneuropathy after chemotherapy), or disorders unrelated to the cancer (eg, discogenic low back pain, arthritis). As Foley[32] has pointed out, these contextual distinctions influence the meaning of pain to the patient. As a result, the degree of suffering experienced and the patient’s ability to cope vary considerably depending, respectively, on whether the pain is regarded as life-threatening, a barrier to rehabilitation, or simply a chronic annoyance.

Prevalence of Breakthrough Pain
Breakthrough pain has only recently been recognized as a distinct clinical entity. Relatively few studies describe this phenomenon in detail, and, thus, its prevalence is difficult to ascertain. Although numerous researchers refer to the number of patients experiencing breakthrough pain (Table 2) as an incidental finding in the course of studies evaluating other aspects of cancer pain,[22,33,34] Portenoy and Hagen[21] are the only investigators who have conducted a prospective evaluation of breakthrough pain in cancer patients. Breakthrough pain has not been formally evaluated in populations of noncancer patients.

Studies Explicitly Evaluating Breakthrough Pain
To date, Portenoy and Hagen’s study[21] provides the most careful characterization of breakthrough pain (Table 3). These investigators evaluated all adult inpatients referred to a pain service at a comprehensive cancer center over a 3-month period. Of this cadre of 90 patients, 70 met the investigators’ criteria for stable analgesic dosing (dose increases of no more than 20% per day for 48 hours), 63 of whom were determined to have well-controlled baseline pain (defined as pain of moderate intensity or less). Of these 63 patients, 41 (63%) met the study’s criteria for the presence
of breakthrough pain (temporary flares of severe or excruciating pain) and were surveyed regarding the nature of the breakthrough pain that they experienced over the prior 24 hours. Of the 51 breakthrough pain episodes, 55% were identified as incident pain and 29% as end-of-dose failure. End-of-dose failure and incident pain (mixed breakthrough pain) were concomitantly present in 43% of pain episodes, and 45% of episodes were idiopathic in nature. Three-quarters of breakthrough pain episodes appeared to be directly related to tumor activity, with most of the remaining episodes presumed to be due to antitumor therapy. Breakthrough pain appeared to be mediated by a variety of underlying mechanisms, and almost all of the episodes occurred in the same location as patients' baseline pain.

The median number of breakthrough pains over a 24-hour period was 4 (range, 1 to 3,600 pains), and about one-fourth of patients identified more than one distinct type of breakthrough pain. Breakthrough pain arose rapidly (< 3 minutes) in 43% of patients and more gradually (> 3 minutes) in the remainder. The median duration of breakthrough pain was 30 minutes, and 41% of the episodes were both of rapid onset and brief duration. Data on duration are presumably influenced by the routine in-hospital use of breakthrough pain medications; the 30-minute median duration observed is consistent with the usual latency-to-effect for standard analgesics.

Bruera and colleagues[9] described their observations on the incidence and nature of incident pain in the context of an open trial on the use of methylphenidate to counter opioid-mediated sedation. In contrast to the study of Portenoy and Hagen,[21] this report's scope was limited to the subset of patients with incident-type breakthrough pain who had already therapeutically achieved "well-controlled pain." Since its focus was the evaluation of a therapeutic intervention, the study by Bruera et al provided fewer details on pain characteristics. Bruera's group screened 118 consecutive patients admitted to an inpatient palliative care unit, all of whom had advanced cancer and pain. They identified 23 patients (19%) with "severe incident pain," of whom 14 were ultimately evaluable. The authors defined incident pain as spontaneous or provoked "severe" acute exacerbations of pain occurring against a background of "good" opioid-mediated pain control. All patients were receiving oral or subcutaneous (SC) morphine or hydromorphone in fixed ATC doses.

Incident pain appeared to be due to bone metastases in 12 (86%) of 14 patients, and was presumed to be related to chest wall invasion and inguinal adenopathy in the remaining 2 patients. Movement appeared to be responsible for provoking pain in all cases: Pain was precipitated by sitting in 2 patients, standing and walking in 2 others, and unspecified movement in the remaining 10 patients (71%).

**Studies Secondarily Evaluating Breakthrough Pain**

As noted, numerous cancer pain studies designed to assess various other aspects of cancer pain refer serendipitously to the incidence and management of breakthrough pain. Although such studies cannot be expected to provide as reliable or detailed data as those designed specifically to investigate these phenomena, because of the overall paucity of applicable data, selected results are summarized briefly here.

Reporting on 184 evaluable consecutive consultations for cancer pain, Banning et al[10] noted that 172 patients (93%) experienced exacerbations of pain with movement (incident pain), and that 124 (67%) reported that pain interrupted their sleep. After 1 to 2 weeks of treatment, movement-related pain resolved in about one-third of the 131 affected patients available for reevaluation. The severity of incident pain was rated as mild, moderate, and severe by 27 (21%), 20 (15%), and 36 (27%) patients, respectively.

Mercadante et al[6] evaluated 98 opioid-naive outpatients with severe or intolerable cancer pain in a trial intended to determine the influence of pain mechanisms, analgesic responsiveness, and movement-related pain on the outcome of treatment based on the World Health Organizations (WHO) analgesic ladder methodology. Overall, 30% of the 98 patients in this study reported experiencing incident-type breakthrough pain. Of patients whose pain persisted despite nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, two-thirds (16 out of 24) reported incident pain. In the course of prospectively evaluating the mechanistic aspects of pain in hospice inpatients, Ashby and coworkers[8] recorded the incidence and severity of "breakthrough pain events" in 20 patients over a mean of 21 days. Breakthrough pain was observed in all but one patient, at a mean frequency of 0.37 events per day (range, 0 to 2.5 events per day).

In a pilot study of oral transmucosal fentanyl citrate (Actiq) for the management of breakthrough pain, Fine et al[35] evaluated 10 inpatients with advanced cancer over a 2-day interval. Although patients' baseline regimen of opioids was not reported, their median visual analog pain intensity was 60 out of 100. Patients experienced a mean of 2.1 episodes of breakthrough pain per day, all
between the hours of 7 am and 7 pm.
Although interpretation of these data is limited by study design and sample size, the data support
the conclusion that breakthrough pain is a common phenomenon in patients with chronic pain. It is
not surprising that reported incidences of breakthrough pain vary considerably, given variations in
study populations and operational definitions of pain phenomena.

**Populations With "Stable" Pain Control**—A recent trend in clinical research involves reliance on
the incidence of breakthrough pain as a reflection of analgesic efficacy, especially in studies that
evaluate long-acting or controlled-release formulations of opioids. Although it is tempting to
extrapolate the results of these studies to characterize the incidence of breakthrough pain, cautious
interpretation is warranted. One limitation is that most of these studies fail to define breakthrough
pain clearly, beyond the need for unscheduled doses of opioids.
Most importantly, however, efficacy studies confine their scope to highly discrete populations and
thus fail to depict the global phenomenon of breakthrough pain. To ensure homogeneity among
groups and reduce confounding variables, entry is usually limited to patients with "stable" pain
(usually defined as fewer than two to three episodes of breakthrough pain daily), usually as
established during a prestudy stabilization or "run-in" period.
Several dose equivalency and proportionality studies have compared the time-contingent
administration of various oral formulations of controlled-release and immediate-release
morphine.[11,33,36,37] The results of these representative studies suggest that cancer patients who
are preselected for well-controlled pain and who are treated in closely supervised settings by expert
clinicians may experience as few as 0.2 to 0.48 daily episodes of breakthrough pain.
Studies of other controlled-release opioid preparations administered to populations with stable
cancer pain yield similar results. A study of twice-daily administration of oral controlled-release
hydromorphone vs intermediate-release hydromorphone administered every 4 hours in 48 patients
with chronic cancer pain reported an average of one episode of breakthrough pain per patient per
day.[22] Another study that compared a controlled-release formulation of rectal morphine with SC
morphine given every 4 hours in 23 patients reported a mean of 1.2 daily episodes of breakthrough
pain per day in both treatment arms.[12]

**Populations With Less Stable Pain Control**—As would be expected, evaluations of drug therapy
in unstratified medical populations with less stable pain control typically reveal higher incidences of
breakthrough pain. A study of a new preparation of controlled-release oral codeine administered
every 12 hours conducted in 30 patients with chronic nonmalignant pain of at least moderate
severity revealed an average of 3.6 episodes and 6 daily episodes of breakthrough pain with active
and placebo (plus prn) treatment, respectively.[38] During an evaluation of transdermal fentanyl in
10 home hospice patients with pain due to advanced metastatic cancer, Herbst et al.[39] reported
that 1 in 10 and 2 in 6 patients had in excess of two episodes of breakthrough pain per day at weeks
2 and 4, respectively, despite adjustments in the transdermal dose.
In a double-dummy crossover comparison of continuous intravenous (IV) and SC hydromorphone
doses administered to 15 hospitalized cancer patients with "stable" but severe pain (732 oral
morphine sulfate equivalents per day), a mean of 5 prn doses was used over each of the
investigation’s 48-hour study intervals, independent of route of administration.[34] In a similar study
comparing continuous SC hydromorphone supplemented with either patient-administered or
nurse-administered boluses of analgesia, patients with advanced cancer in an inpatient palliative
care unit experienced a mean of 1 and 0.36 daily episodes of breakthrough pain, respectively.[40]

**Incident Pain as a Predictor of Poor Outcome**
As noted, several investigators have attempted to identify factors that predict poor response to
pharmacotherapy. By helping the clinician identify patients at risk for treatment failure,
multidisciplinary treatment can be integrated prospectively. In addition, stratifying patients
according to the presence of specific problem pain scenarios facilitates the development of clinical
practice protocols and allows the results of research to be applied with greater certainty to individual
patients.
These lines of research associated breakthrough pain (specifically, incident or movement-related
pain) with an increased likelihood of treatment failure. In a validation study of the Edmonton staging
system for cancer pain, Bruera and colleagues[5] identified five features that were predictive of poor
outcome, and excluded two other features as predictors (Table 4). This schema utilizes an
alphanumeric coding system similar to clinicohistologic schemata applied to stage tumors.[41] In
addition to incident pain, neuropathic pain, tolerance to opioids, a history of alcohol or drug abuse,
and psychological distress were predictive of a poor outcome, while opioid dose and the presence of confusion were not significantly predictive.

In a prospective study of pain characteristics in 52 patients with lung cancer, Mercadante et al[7] distinguished incident pain as the only clinical feature that reliably correlated with treatment failure. In a separate study that endeavored to determine the influence of pain mechanism on responsiveness to WHO-endorsed analgesics in 98 palliative-care patients, Mercadante et al[6] also identified incident pain as the only positive predictive feature. Finally, Ashby et al[8] isolated incident pain as the only feature predictive of poor outcome in a study of 20 hospitalized palliative-care patients with significant pain. Interestingly, the last three studies cited were unable to establish a correlation between the presence of neuropathic pain and outcome.

**Clinical Significance of Breakthrough Pain**

The assessment and management of breakthrough pain should be considered in the development of a patient’s overall pain management strategy. As breakthrough pain is a heterogenous phenomenon, clinical decision-making depends on eliciting its pattern. Since opioid therapy rarely eliminates pain entirely and more commonly involves achieving a favorable balance between comfort and side effects, some degree of breakthrough pain is usually inevitable, but it is not necessarily problematic. Breakthrough pain that is mild, infrequent, or slow to arise is generally well tolerated and manageable. Severe, distressing, frequent or rapid-onset breakthrough pain, however, should be identified, assessed, and aggressively managed.

In some cases, infrequent, low-level breakthrough pain may be more desirable than a dosing schema that is intended to eliminate pain exacerbations entirely but that results in relative opioid overdose between flares. Slowly mounting breakthrough pain may either reflect the development of tolerance or indolent tumor progression. Sudden increases in the frequency or severity of breakthrough pain or its occurrence in new sites should alert the clinician to the possibility of rapid tumor or disease progression, new metastases, or other events, such as impending or pathologic fracture. Although it should be treated, breakthrough pain that occurs during recovery from surgery or prolonged bed rest is expected and suggests compliance with the rehabilitation plan. Modest changes in the pattern of breakthrough pain in an otherwise stable cancer patient are regarded as the best gauge for adjusting the dose or schedule of the basal analgesic.

**Cancer Pain Guidelines and Breakthrough Pain**

Multiple guidelines have been developed for the treatment of cancer pain that rely, whenever possible, on outcome data from controlled or partially controlled investigations. However, optimal management of breakthrough pain remains largely empiric and not evidence-based. Guidelines developed by the WHO[42] have been widely accepted and are the basis for newer efforts. The WHO guidelines employ a primary strategy of matching analgesic potency with pain intensity (ie, NSAIDs for mild pain and various opioids for moderate to severe pain) and secondarily selecting drugs based on the presumed mechanisms of pain (eg, NSAIDs and opioids for nociceptive pain and adjuvants for neuropathic pain). These guidelines do not specifically address breakthrough pain, however.

Guidelines developed more recently by the Agency for Health Care Policy and Research (AHCPR)[2] endorse the principles of the WHO guidelines and further recommend the administration of regularly scheduled analgesic doses (ie, ATC agents), as well as additional doses of breakthrough pain medication. The AHCPR guidelines do not provide specific recommendations for selecting drugs or drug doses to treat breakthrough pain. However, researchers have reported on the clinical outcomes of series of patients whose breakthrough pain has been managed with various protocols. Although expert recommendations have evolved from these experiences, more highly focused research is required to establish evidence-based guidelines.

**Current Regimens for Managing Breakthrough Pain**

**Oral and Transdermal Administration**

Oral[2,4,42] and transdermal[2] routes of administration of opioid analgesics are recommended for the management of chronic cancer pain, when possible (Figure 1). These routes are preferred because they promote patient independence, do not require special nursing and pharmacy care, and are convenient and cost-effective.

A single-entity pure opioid agonist with a relatively short latency-to-onset period and brief duration
of action is typically recommended to treat breakthrough pain in patients whose basal pain is controlled with scheduled doses of long-acting oral or transdermal opioids. Currently available agents include immediate-release oral morphine, hydromorphone, and oxycodone, provided in tablet or liquid formulations.

Of these preparations, immediate-release morphine is most commonly prescribed. Oral morphine is widely used in the treatment of both persistent baseline and breakthrough pain, predominantly because of its worldwide availability, short half-life, predictable linear pharmacokinetics, and long history of successful use.[43] It is generally recommended that, when available and affordable, an immediate-release formulation similar to the long-acting opioid formulation be used for breakthrough pain. This will decrease the number of opioid-related side effects that may occur.

**Parenteral Administration**

Because of its cost, invasiveness, and requirement for sophisticated nursing and pharmacy interventions, parenteral (other than transdermal) administration of opioids is typically reserved for specific indications. These include short-term use for unstable pain, continuous use for end-of-life care when other forms cannot be used due to inability to swallow, and chronic use for compromised gastrointestinal function (eg, chronic nausea and vomiting, dysphagia, alimentary tract obstruction, malabsorption, and delirium).

The chronic administration of injectable or infusional opioid analgesics is most commonly undertaken with morphine or hydromorphone. Morphine is used primarily for the same reasons that it is preferred for oral administration. Hydromorphone is usually selected when the patient has a history of intolerance to morphine or, because it is more soluble than morphine, for high-dose subcutaneous administration. Once reserved for inpatient use, fentanyl citrate[44] and even sufentanil (Sufental)[45] have recently been suggested as safe and effective alternatives for chronic use as well. Due to its ease of administration, the SC route has emerged as the parenteral route of choice, except when an indwelling IV catheter is already present.[46]

**Supplemental prn Doses**—Constant infusions are usually supplemented with prn doses administered in response to patient demand (patient-controlled analgesia [PCA]). Whenever possible, constant infusions of an opioid are supplemented with prn doses of the same agent in order to avoid potential problems with multiple-agent toxicity and calculation errors as well as for ease of administration. These supplemental doses are typically expressed as a percentage of the fixed hourly administration rate. Most infusion pumps suitable for the administration of analgesics have a feature that restricts the minimum interval between patient-administered boluses (lock-out interval), rendering the system ultimately subject to physician control.

The frequency and dose of parenteral prn drugs prescribed in clinical practice are also contingent on available technology.[47] For example, the sophisticated infusion devices available in acute-care settings permit the use of short lock-out intervals (eg, 10 to 15 minutes) between prn doses, while the simpler, less costly infusion pumps used in hospice and home care cannot be programmed to dose that frequently. Indeed, PCA may not be available at all in hospice and home care settings. These pragmatic considerations account for reports of regimens that rely on frequent adjustments of the continuous rate to maintain comfort in lieu of the provision of patient-administered boluses. Reviews of continuous parenteral infusions supplemented by PCA or nurse-administered boluses recommend the provision of prn doses ranging from 50% to 200% of the hourly infusion rate at intervals ranging from every 15 minutes to every 2 hours.[40,46,48-50] For example, using prn doses equal to 25% of the hourly infusion rate, Swanson et al[51] reported effective pain relief in 95% of 117 ambulatory cancer patients managed with IV or SC opioids administered via PCA. In another report, Vanier et al[52] utilized prn doses of SC hydromorphone equal to the hourly infusion rate provided as often as every 60 minutes.

**Contemporary Management**

Portenoy and Hagen[21] recommend that the management of breakthrough cancer pain be based on the following four basic principles:

1. Comprehensive assessment, including evaluation of the characteristics, etiology, and pathophysiology of pain, as well as the relationship of pain to the patient’s overall clinical status

2. Consideration of the underlying etiology of pain

3. Individual adjustment of the analgesic regimen (eg, adjustment of breakthrough pain doses and ATC regimens)
By elucidating the causes of pain, a comprehensive evaluation may suggest therapeutic interventions, such as chemotherapy, radiotherapy, radionuclides, surgical excision, or orthopedic stabilization that, when implemented, may resolve pain or simplify its pharmacologic management. For example, external-beam radiation therapy or the administration of a therapeutic radionuclide may improve breakthrough pain that is due to bone metastases, and surgery or external stabilization may decrease breakthrough pain due to pathologic fracture. Likewise, palliative anesthetic or neurosurgical options may be indicated for specific troublesome pain syndromes, such as abdominal pain due to pancreatic cancer or localized rib pain. In addition, assessment may identify environmental and psychological mediators of pain that can be addressed with behavioral or rehabilitative interventions.

Although the literature supports opioids as the treatment of choice for breakthrough pain, other interventions have important adjunctive roles in specific settings. Pain of neuropathic origin may be less opioid-responsive than nociceptive pain and often responds favorably to the addition of a variety of adjuvant analgesics (eg, antidepressants and anticonvulsants). Corticosteroids have been reported to be effective in patients with poorly controlled pain due to bone metastases or plexopathy. A variety of other adjuvant agents, such as antispasmodics for muscle pain and antiperistaltic drugs, can be helpful in specific settings. Finally, despite similar pharmacodynamic effects, the efficacy and side effect profiles of opioids differ idiosyncratically among patients, and, as a result, substitution of one opioid agonist for another may improve pain control or lessen opioid-induced toxicity.

**Optimal Opioid Use**—Optimal management of breakthrough pain with opioids is contingent on the pain’s specific features. Breakthrough pain that is temporally related to scheduled doses of long-acting opioids is empirically managed by adjusting the dose or schedule of the basal ATC analgesic. When feasible, a dose increase with maintenance of the interval between administrations is preferred, in order to maximize the convenience conferred by long-acting agents. Changes observed in response to such adjustments help confirm the presence or absence of end-of-dose failure as an explanation for breakthrough pain. If such adjustments are met with new side effects that are unremitting, consideration may be given to a trial of an alternate ATC opioid. In contrast to end-of-dose failure, other types of breakthrough pain are typically best managed by adjusting the breakthrough, or prn, pain medication component of opioid therapy. Both incident and idiopathic breakthrough pain are usually managed with prn administration of short-acting opioids (ie, intermediate-release morphine, hydromorphone, or oxycodone). Drug selection is empiric, although it is generally preferred to supplement the basal analgesic with prn doses of the same drug, administered by the same route, except when no short-acting analog is available (eg, methadone, levorphanol [Levo-Dromoran], and transdermal fentanyl).

By convention, the selection of the initial dose of breakthrough pain medication reflects and is roughly proportional to the dose of the basal analgesic. Most authorities advocate commencing with breakthrough pain doses equivalent to 5% to 15% of the total daily ATC opioid dosage administered every 2 to 4 hours. This regimen appears to be generally safe and effective, and can be further adjusted based on the patient’s reports of efficacy and side effects.

When incident pain is relatively predictable, patients should be encouraged to use breakthrough pain medications prophylactically, usually about 30 minutes in advance of the pain-provoking activity. When unanticipated breakthrough pain occurs, the breakthrough pain medication should be taken as soon after onset as possible, even when this coincides with the time for a scheduled dose of the patient’s basal analgesic. If these strategies are unsuccessful, a trial of an alternate short-acting opioid or a change in route should be considered. Breakthrough pain that is predictable, infrequent, of mild or moderate intensity, or slow to develop can usually be managed effectively with oral analgesics, such as intermediate-release morphine, hydromorphone, or oxycodone. Breakthrough pain that is severe or that occurs unpredictably, frequently, or precipitously may not be adequately relieved with currently available oral or rectal agents. Typically, incident pain related to movement is especially challenging to manage because opioid requirements vary dramatically over short intervals. Doses of opioids that are adequate to treat pain during periods of rest are insufficient when activity increases; conversely, doses required to ease movement-related pain may produce sedation and other side effects when the provocative activity ceases. As a result, refractory incident pain is a frequent indication for parenteral drug administration or...
anesthetic/neurosurgical procedures. Although IV and SC opioids are pharmacokinetically well-suited to the treatment of labile and/or severe breakthrough pain, especially that due to movement, these advantages are offset by their invasiveness. Oral agents in current use may be of benefit, but onset of analgesia is more delayed. **Transmucosal Fentanyl**—A new form of orally administered fentanyl appears to be a promising solution for managing refractory breakthrough pain, especially when it is rapid in onset, as is the case for incident (movement-related) pain. Oral transmucosal fentanyl citrate, a solid formulation of fentanyl citrate consisting of a drug-impregnated matrix on a plastic holder, is a noninvasive means of delivering the potent analgesic fentanyl through the oral mucosa. This oral transmucosal formulation is rapidly absorbed and produces analgesia of quick onset (5 to 10 minutes) and short duration,[64-67] although analgesic duration is slightly prolonged as a result of the small proportion of fentanyl that is swallowed and subject to the hepatic first-pass effect. Oral transmucosal fentanyl citrate is currently approved only to promote analgesia and sedation prior to painful procedures in supervised settings. Pilot research suggests, however, that it may be superior to traditional breakthrough pain analgesics for treating breakthrough pain in cancer patients maintained on chronic opioid therapy. In double-blind, randomized, parallel studies, patients maintained on long-acting preparations of oral morphine or transdermal fentanyl reported more rapid and satisfactory relief of breakthrough pain when transmucosal fentanyl was substituted for their regular breakthrough pain medications. Further studies should better define the role of this preparation in the treatment of breakthrough pain.

**Conclusions**

Careful assessment is essential for optimal cancer pain management. As part of that assessment, the clinician should elicit information on the pain's temporal features and should question patients about the presence and characteristics of breakthrough pain. An understanding of the tempo of pain will aid the clinician in establishing an optimal treatment regimen. Although the clinical importance of breakthrough pain has been repeatedly emphasized, this and other concepts related to the temporal aspects of chronic pain have only recently been addressed in the medical literature. Further data are required to provide a clearer understanding of the prevalence and characteristics of breakthrough pain in cancer, as well as optimal ways to control this common, troublesome symptom.

**References:**


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