Chapter 2

What is cancer breakthrough pain?

Definitions

The original definition of cancer breakthrough pain (cBTP), given by Portenoy and Hagen [1], is the template upon which the majority of subsequent definitions have been based: breakthrough pain (BTP) is a transitory increase in pain to greater than moderate intensity on a baseline pain of moderate intensity or less. Other authors have modified this definition in a number of ways but the majority of authors require that the background, baseline, or persistent pain be adequately controlled in-line with the original definition given by Portenoy and Hagen. Similarly, the definition of cBTP used in this text requires adequately controlled baseline pain as well:

> *"cBTP 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 [2,3]."*

Note that by definition, for a particular flare of pain to be cBTP, the patient must have cancer; however, the actual source of the pain may or may not be directly related to the cancer. For example, the pain may be secondary to chemotherapy or other cancer-related treatments, tumor invasion of bone or nerve, a herniated disc, or osteoarthritis [4,5].*

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Adequate pain control

Twycross has described pain control in the hospice setting and developed the practical concept of "good enough" pain relief [3,6]. Pain relief is "good enough" when the patient can accomplish desired rational goals without undue suffering. It is ideal if complete pain relief can be achieved without unacceptable side effects. However, sometimes cancer pain does not respond completely to analgesics, surgery, nerve blocks, or cancer-directed therapy; in other words, the patient's pain may not be completely eliminated. In these cases, clinicians must seek "good enough" pain relief for the patient. The clinician must help the patient understand what rational goals are based on the patient's current state of health. Adequately controlled pain will usually correspond to a pain score of 0–4 on the Numerical Rating Scale, where 0 represents no pain and 10 represents the worst imaginable pain [7].

Cancer breakthrough pain versus background pain flares

In addition to understanding the concept of "adequate control", it is also imperative that the clinician be able to distinguish cBTP from background pain flares (BGPF). Most authors consider the "breaking through" aspect of cBTP to be the pain overriding the otherwise stable control of the patient's basal or background pain (Figure 2.1A[†]) [8–10]. Persistent pain and cBTP are distinct clinical entities and should be assessed individually [10]. Basal, background, or persistent pain for patients with cBTP usually lasts longer than 12 hours/day and is adequately controlled by an around-the-clock (ATC) analgesic medication, usually an opioid. However, a flare of pain or a BGPF (Figure 2.1B[†]) occurs when the background pain is not under

**Some authors have protested creating a separate category for cancer pain and contend that cancer pain should be considered under the categories of either acute or chronic pain. While the discussion of the advantages and disadvantages of defining cancer pain as somehow distinct from other forms of acute or chronic pain will not be expanded upon here, the fact that cancer pain management often blends into palliative care and end-of-life care adds a unique dimension to cancer pain management [5].*

[†]When looking at pain versus time diagrams (Figures 2.1A, B), it should be noted that the height of the background pain line reflects the intensity of the pain prior to treatment rather than the actual current pain level. Since, by definition, cBTP requires that the background, persistent pain is adequately controlled all the pain diagrams would show a low-basal pain if the current basal pain were represented; however, this would not add any information to the diagrams. This contrivance of representing the basal-pain level prior to treatment in these diagrams helps give a better picture of

adequate control [2]. In contrast to Figure 2.1A, where the background pain is under adequate control, Figure 2.1B shows poorly controlled, persistent background pain and a flare of pain. Rescue pain medications, generally short-acting opioids (SAOs), are used to treat BGPFs, whereas both SAOs and rapid-onset opioids (ROOs) may be used to treat cBTP.

In a sense, the origin of cBTP management lies in the use of rescue medication as a method of titration of the ATC analgesic. This evolution of cancer pain management and the similarity of cBTP episodes to flares of pain seen in patients without adequately controlled background pain has led to some disagreement in the literature about the terminology of cBTP. Unfortunately, there is not a universally agreed upon terminology for cBTP management [11] and it is not uncommon to see the term "rescue dose" or "rescue medication" and "breakthrough dose" or "breakthrough medication" used interchangeably in the literature [2,8,12]. This can create some confusion. Readers may see the term "rescue dose" applied to a ROO used to treat spontaneous cBTP or see the term "breakthrough dose" used to refer to the use of morphine for titration of the ATC analgesic dose. When reading publications about cBTP, the reader should determine how the terms were defined within the text to establish the author's true meaning.

Differential diagnoses

Intermittent pain or nonbreakthrough pain

A study by Mystakidou et al investigated patients with cancer who did not have background pain but who had intermittent flares of pain [13]. Although this pain is very similar in characteristics to cBTP, as there is

the overall pain state of the patient. If the basal pain is adequately controlled then the basal analgesic line is drawn above the basal pain line (Figure 2.1A). If the basal pain is not adequately controlled then the basal analgesic line is drawn below the basal pain line (Figure 2.1B). It is hoped that these simple pain versus time diagrams can help clinicians and healthcare professionals better conceptualize a framework for managing cancer pain. Constructing a pain versus time diagram may help the clinician determine an appropriate analgesic regimen for a patient. The time intervals are not specified in Figures 2.1A, B because the time interval between cBTP episodes can vary from minutes to hours to days. Rather, in clinical practice it is important to know when the cBTP occurs in relation to other life events. As will be discussed later in the text, the time interval between cBTP episodes is one of the criteria that are used in determining whether it is appropriate to treat each cBTP episode individually or whether the basal analgesic should be increased. This can also help with detecting end-of-dose failure and incident pain.

Depiction of a cancer breakthrough pain episode

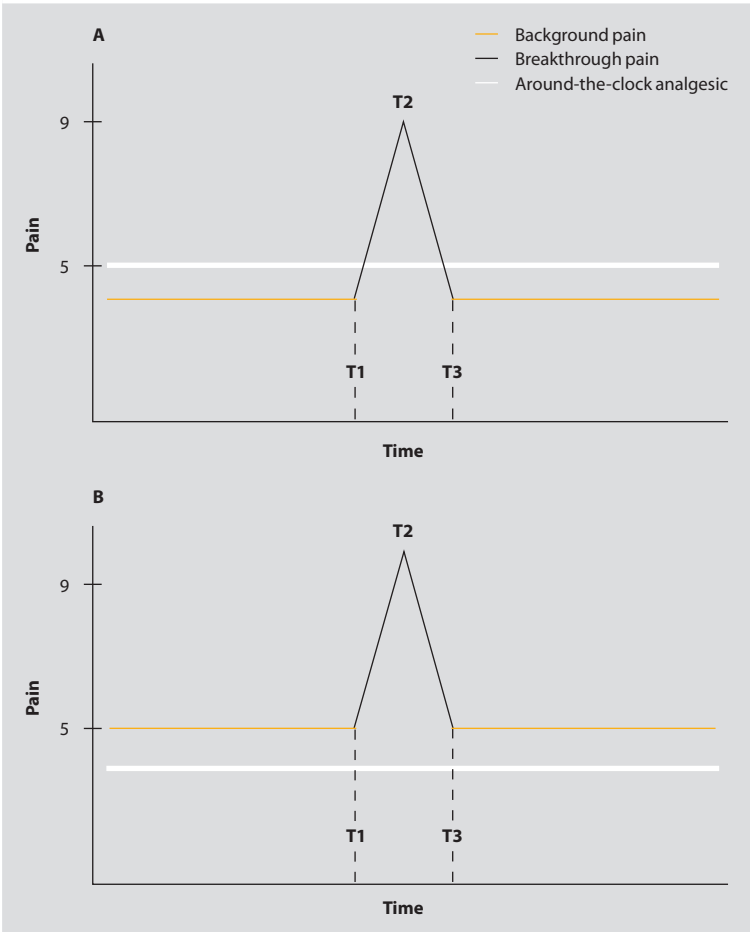


Figure 2.1 Depiction of a cancer breakthrough pain episode. A, Cancer breakthrough pain with stable background pain. The patient's pain is under stable, adequate control (background pain is ≤4 out of 10 on the NRS) since the background pain line is below the around-the-clock analgesic line. At T1, the patient experiences a sudden, rapid increase in pain that "breaks through" the around-the-clock analgesic; this cancer breakthrough pain episode peaks at 9 out of 10 on the NRS at T2; T3 represents how long the breakthrough pain lasts. Note that an analgesic line above the basal pain line does not mean that the basal pain has been reduced to zero but rather that the background pain is adequately controlled (≤4 out of 10 on NRS). **B**, Cancer background pain flare, without adequate control. The patient's pain is not under adequate control since the around-the-clock analgesic line is below the patient's background pain line. At T1, the patient experiences a sudden, rapid increase of pain, which peaks at 9 out of 10 on the NRS (T2) and last until T3. This is known as a background pain flare. NRS, Numerical Rating Scale.

no background pain, it is by definition not cBTP or a BGPF; the authors have instead suggested the names "intermittent pain" or "nonbreakthrough pain" [13]. There are very few studies on nonbreakthrough cancer pain; it is only mentioned here for completeness and so that the practitioner will recognize that while these flares of nonbreakthrough pain may seem like cBTP, they are not.

End-of-dose failure

Some authors have included end-of-dose failure as a form of pseudo-cBTP that occurs when the dosing interval between long-acting agents is longer than the effective duration of the drug [14]. The drug level falls too low before the next dose is administered to provide analgesic coverage and the patient experiences pain [15]. This type of pain is not actually cBTP and is best managed by addressing the frequency or dose of ATC basal analgesic rather than by adding a cBTP medication [16–18]. For this reason, other authors, including myself [2], have not included end-of-dose failure as a form of cBTP [3].

Characteristics of cancer breakthrough pain

Studies show that cBTP occurs in 40–80% of patients with cancer-related pain [19,20]. Thus, its severity and frequency of occurrence underscore the relevance of cBTP treatment in the overall management of cancer pain [21,22]. cBTP is generally of moderate-to-severe intensity, with a rapid onset of 3–15 minutes. Episodes last for approximately 60 minutes (Table 2.1, Figure 2.1A), but can range in duration from 1 to 240 minutes [23]. cBTP episodes occur approximately 3–5 times per day [14,23,24].

Characteristics of cancer breakthrough pain

Characteristics of cBTP	Average
Time-to-peak severity	3–15 minutes
Severity	Moderate to severe
Duration	30–60 minutes
Number of episodes per day	3–5

Table 2.1 Characteristics of cancer breakthrough pain. cBTP is a transitory pain that "breaks through" background or persistent pain, which is adequately controlled by an around-the-clock medication. cBTP, cancer breakthrough pain.

Types of cancer breakthrough pain

There are two main types of cBTP: predictable and spontaneous (idiopathic) or unpredictable (Table 2.2) [3]. Predictable cBTP is most often due to movement and it has an understandable cause. Spontaneous cBTP occurs without warning and is not associated with any particular event or activity. It has no identifiable cause and it does not have a consistent temporal relationship between the cBTP pain episode, basal analgesic dose, or activity. In a multicenter European study involving 320 patients with cancer, 44% of patients reported experiencing incident-related or predictable cBTP, 39% had spontaneous cBTP, and 17% reported having both types of cBTP [24].

Assessment of cancer breakthrough pain

Before initiating treatment for a patient with suspected cBTP, a physician should first confirm that the patient has cancer and the patient's background pain is under adequate control [10]. Once that is confirmed, one of the first steps in assessing cBTP is to educate the patient about the definition of both cBTP and background pain [25]. This educational process will help the patient and physician establish a common language for discussing the patient's pain.

A number of tools have been developed for the assessment of cBTP, but none are currently widely used in clinical practice [8]. Haugen et al [8] reviewed available global literature on the assessment of cBTP and concluded that ideally the clinician should determine:

- the number of cBTP episodes;
- the relationship between cBTP and the background pain (the same or different);
- the intensity of the cBTP episodes;

Type of cancer breakthrough pain

Type of cancer breakthrough pain	Characteristics
Predictable	Consistent temporal relationship with precipitating factor
Spontaneous (idiopathic) or unpredictable	Not induced by a readily identifiable cause; inconsistent temporal relationship with a precipitating factor

Table 2.2 Types of cancer breakthrough pain. Data from Bennett et al [3].

- the temporal factors of cBTP; including its frequency, onset, duration, and relationship to fixed analgesic dose;
- where cBTP episodes are occurring in the body;
- the quality of the cBTP (eg, burning, aching, lancinating, throbbing);
- any potential treatment-related factors, including exacerbating and relieving factors, such as precipitating events and predictability, response to treatment (time-to-meaningful relief), and treatment satisfaction; and
- whether the cBTP interferes with activities of daily living and quality of life.

An assessment tool is available (see page 20) that incorporates many of these features [3,8]. The topics not specifically covered within the assessment form and deemed important by the clinician can be included during the patient interview or added as additional questions to the tool.

More discussion regarding a practical approach to assessment and diagnosis of patients with suspected cBTP will be further described through case studies in Chapter 4.

Understanding cancer breakthrough pain and its treatment

Once a patient's cBTP has been confirmed and fully assessed, several treatment options may be pursued. First and foremost, since cBTP varies per patient, the treatment must be individualized and tailored to each patient's specific needs (like the World Health Organization recommends "for the individual" and with "attention to detail"). Depending on the patient's cBTP, nonpharmacological methods (eg, heat, ice, distraction, guided imagery, massage, or transcutaneous electrical nerve stimulation [TENS]) [26,27] may be used to manage their cBTP. However, if nonpharmacological approaches are not sufficient, there are a number of pharmacological approaches, specifically ROOs, available based on the varying types, frequencies, durations, and temporal profiles of a patient's cBTP. As ROOs are currently the only medications approved for the treatment of cBTP, this class will be discussed in general terms below, and specific ROOs will be further explored in Chapter 3.

Initial cancer breakthrough pain assessment

Name: Date:

1. Do you have episodes of severe pain or breakthrough pain?

2. Please refer to the diagram (right) to answer the next questions. Is your pain more like Peak 1 (which rapidly peaks in intensity) or Peak 2 (which peaks gradually in intensity overtime)?

A. How long does the pain last on average? Peak 1: _____ Peak 2: _____

B. Do you have some episodes of both Peak 1 and Peak 2? Yes ☐ No ☐

Answer the following three questions on a scale of 0–10; 0 represents no pain and 10 represents the worst imaginable pain

3. Rate your average background pain over the past 24 hours:

4. Rate your average breakthrough pain intensity over the past 24 hours:

5. Rate the maximum intensity of your breakthrough pain in the past 24 hours:

6. How many breakthrough pain episodes have you had over the past 24 hours?

7. If you have multiple breakthrough pain episodes, how long does each episode of breakthrough pain last?

8. How long is it from the time the pain first occurs to when the pain is at its worst?

9. Where does the breakthrough pain occur? What does it feel like?

Explain:

10. Is your breakthrough pain the same type of pain as your background pain or is it different?

Explain:

11. Do you have more than one type of breakthrough pain? Yes ☐ No ☐

If yes, explain:

12. Do you have breakthrough pain with specific movements of activities? Yes ☐ No ☐

If yes, explain:

13. Does your breakthrough pain occur spontaneously or for no apparent reason? Yes ☐ No ☐

If yes, explain:

14. Does your breakthrough pain occur just before you are supposed to take your next dose of pain medicine? Yes ☐ No ☐

If yes, explain:

15. Does your breakthrough pain have any relation to the time of day? Yes ☐ No ☐

If yes, explain:

16. What impact does the breakthrough pain have on your daily activities at home/work? Are you able to do the things you want/need to do?

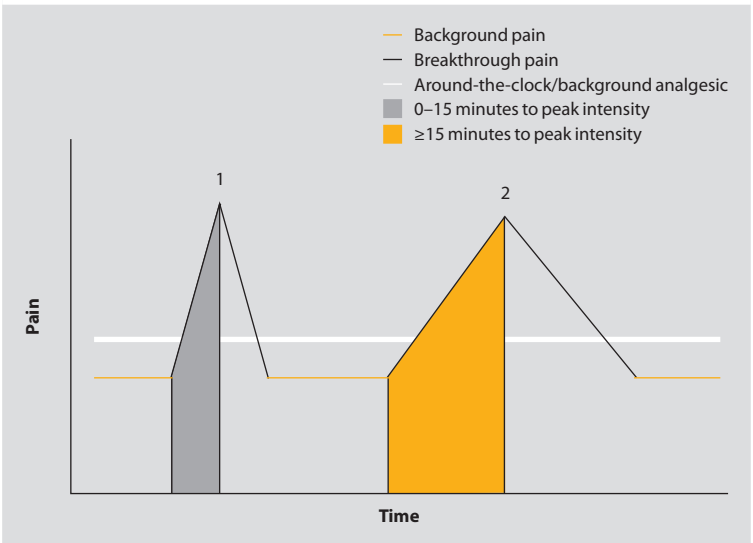
17. Are there any things that you avoid doing or that you are able to do only with severe pain?

18. What do you do to relieve the breakthrough pain?

19. What types of treatment and/or drugs have you used? How long did you use them? Were they effective? Are they still effective?

Describe your current breakthrough pain treatment (if any):

Initial cancer breakthrough pain assessment (continued)



Different types of cancer breakthrough pain episodes in relation to treatment

Cancer breakthrough pain and background pain flares

Understanding the difference between cBTP and BGPF, as described in Figures 2.1A and 2.1B, is critical for determining the pharmacological approach that will be most appropriate for the patient. The dose of medication used for treating a BGPF – know as a "rescue dose" – is usually incorporated into the daily ATC dose for background pain management during dose titration. However, ROOs are titrated to control cBTP and they are not incorporated into the ATC background pain medication since the background pain should already be under adequate control when a ROO is initiated.

High-basal versus low-basal pain

The basal analgesic dose does not predict the cBTP medication dose. A patient with a high-level of basal pain and associated high-basal analgesic dose could have cBTP episodes of mild intensity (Figure 2.2A) [2,24,28,29], which may only require small doses of cBTP medications, or

nonpharmacological measures to manage the cBTP episodes. Meanwhile, a patient with low-level basal pain and correspondingly low levels of basal analgesic medication could experience high-intensity cBTP episodes, where high doses of cBTP medications may be more appropriate (Figure 2.2B) [2,24,28,29].

In early studies with oral transmucosal fentanyl citrate (OTFC), the first ROO approved for cBTP in the United States, no relationship was found between the successful dose of OTFC and the total daily dose of ATC opioid, indicating that the optimal dose of OTFC could not be

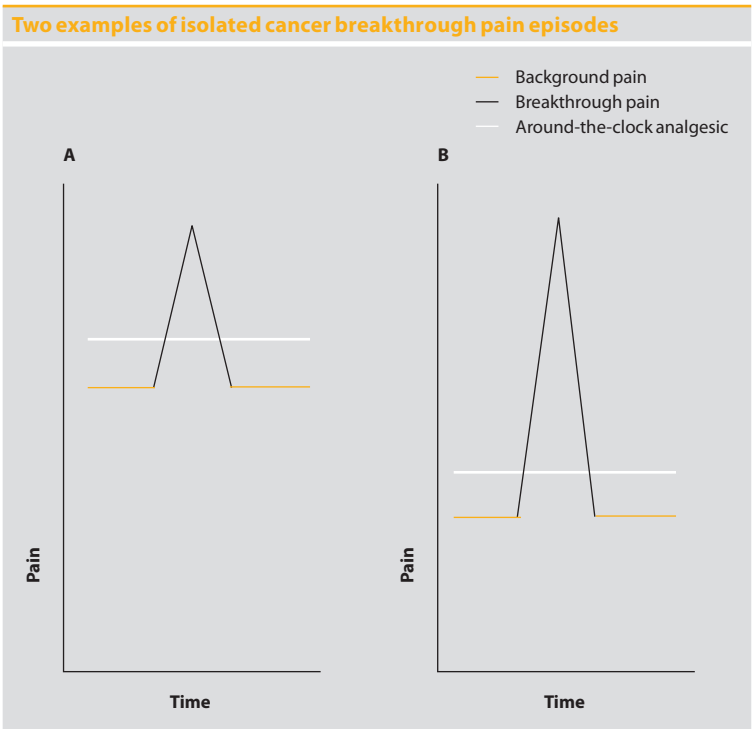


Figure 2.2 Two examples of isolated cancer breakthrough pain episodes. A, The patient has high-level basal pain, requiring a high dose of opioids, while the cBTP episode is of mild intensity and may thus be controlled with a small dose of opioid, and even possibly with nonpharmacological means. **B,** The patient has mild basal pain, but the cBTP episode is of severe intensity and may thus require a high dose of opioid for control. Note: not every cBTP episode requires an opioid for management; not all cBTP episodes are the same, even in the same patient, thus individualization of treatment is mandatory. cBTP, cancer breakthrough pain. Data from Davies et al [2], Davies et al [24], Green et al [28], and Davies et al [29].

predicted by the total daily dose of fixed-schedule opioid for basal pain [14,30]. This led to the recommendation to titrate-to-effect OTFC, starting with the lowest dose and increasing it in a stepwise fashion until cBTP became adequately controlled [31,32]. Similar recommendations have subsequently been made for all of the approved ROOs.

Varying types of cancer breakthrough pain episodes for one patient

Studies have shown that cBTP episodes vary both between individuals and also within individuals [14,24]. In any particular patient, some cBTP episodes may be severe while other episodes may be of minimal intensity. The severe cBTP episodes may require a potent ROO for management, while the less intense episodes might be managed with an SAO or nonpharmacologic techniques, such as heat, ice, distraction, imagery, massage, or TENS [26,27], and, as such, a patient with several types of basal pain and cBTP episodes may therefore require various types of treatment (ie, long-acting opioids [LAO] for basal pain, SAOs, and ROOs). Some physicians may feel uncomfortable with prescribing multiple medications; however, sometimes such treatment plans may be required for optimal results. A physician can tailor the pain management regimen most appropriately for the patient by listening to the patient's needs, the caregiver's input (if applicable), and determining pain patterns and pathophysiology (neuropathic, nociceptive, visceral, and somatic).

Predictable versus spontaneous cancer breakthrough pain and treatment

Predictable and spontaneous cBTP episodes may be managed differently (Table 2.3). Since predictable cBTP has a consistent temporal relationship with an activity, the pain can be preemptively managed with a regular opioid, such as an SAO, taken at least 30–45 minutes prior to the activity that causes the pain [33]. Spontaneous episodes of cBTP require a different approach as these episodes are unpredictable. SAOs have a longer time to onset (30–45 minutes) than ROOs (5–15 minutes), thus ROOs are more appropriate for spontaneous episodes of cBTP (Figure 1.6) [7]. The peak of the analgesic effect with standard opioids, such as oral

Treatment guidelines for predictable and spontaneous cancer breakthrough pain

Type of cancer breakthrough pain	Treatment
Predictable	Preemptive, SAO 30–45 minutes prior to activity
Spontaneous (idiopathic) or unpredictable	ROO or SAO*

Table 2.3 Treatment guidelines for predictable and spontaneous cancer breakthrough pain. *If the pain escalates slowly to maximum intensity, an SAO may be appropriate. ROO, rapid-onset opioid; SAO, short-acting opioid. Data from Bennett et al [3].

morphine, oxycodone, hydromorphone, or methadone, may occur after the pain has resolved [33,34]. Many drugs, such as nasal morphine [35,36], oral methadone [37], nasal sufentanil [38], and subcutaneous hydromorphone [39], have been studied for the treatment of cBTP; however, to date, the only drugs specifically approved for the treatment of cBTP in the United States or the European Union remain fentanyl-based ROOs.

Duration of cancer breakthrough pain episodes and treatment

The duration and time to peak-pain intensity of cBTP episodes also needs to be taken into account when considering treatment. For example, if a cBTP episode is very rapid in onset and very brief in duration (eg, peak intensity occurs in 3–5 minutes and duration of cBTP is 15–30 minutes) it is reasonable to consider using the ROO with the fastest onset time and the shortest duration of action [40]. If the cBTP episode has a slower onset, then a ROO with a slightly slower onset time might be more appropriate. If the cBTP episode is of long duration, several hours or more, then an SAO might be appropriate. The goal is to try to match the time–intensity profile of the cBTP episode with the action profile of the medication used to treat the episode.

Studies of the duration of effect of cBTP medications are complicated by the fact that most cBTP episodes are expected to last for a relatively short period of time and in any patient, episodes can vary in intensity and the frequency of episodes may not be constant [41]. Thus, it is not possible to tell if a cBTP episode was suppressed by an analgesic or if it naturally resolved before the analgesic wore off. For this reason most cBTP studies do not report on the duration of action of the drugs. Nonetheless, duration of ROOs can be judged based on their means of absorption into

the body (eg, oral, additional gastrointestinal absorption, nasal, etc). This will be further discussed in Chapter 3.

Physicians must also take into account that if a drug has a duration of action significantly beyond the duration of the cBTP episode, the risk of adverse effects, such as sedation or respiratory depression, might increase as the drug's sedative and respiratory depressant effects would not be opposed by the cBTP episode during the latter part of its action [9,33]; acute pain antagonizes the respiratory depressant effect of opioids and stimulates respiration [42]. This is another reason to match the drug's time course of action to the time course of the cBTP [43].

Frequency of cancer breakthrough pain episodes and treatment

The frequency of cBTP episodes has implications for treatment. As a general rule, if the patient consistently requires treatment for more than 4 cBTP episodes per day, then the adequacy of the ATC medication should be reassessed [44]. For example, it is reasonable to treat a patient with 4 cBTP episodes per day with an SAO or ROO, depending upon the temporal profile of the cBTP episodes. In contrast, if a patient has, for example, 11 cBTP episodes per day that occur every 2 hours, then taking medication to compensate for each cBTP episode can become burdensome for the patient or caregiver; it may be more appropriate for the patient to increase the ATC medication (eg, LAO) by titration.

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