ISSUE HIGHLIGHTS

Decision-Maker Commentary

Breakthrough Cancer Pain: Ten Commandments

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ABSTRACT

The term “breakthrough cancer pain” (BTcP) was introduced about 25 years ago. Peaks of pain intensity reported in patients with cancer had been invariably examined in the past years, providing relevant information for a better knowledge of this phenomenon and its treatment. The aim of this critical review was to provide the golden rules, namely, the 10 commandments, for a correct diagnostic pathway of BTcP and a consequent personalized pharmacological treatment. These are as follows: 1) assessment of background analgesia, 2) drugs used for background analgesia, 3) BTcP is a frequent phenomenon, 4) characteristics of BTcP, 5) diagnosis of BTcP, 6) continuous assessment, 7) tailored pharmacological treatment of BTcP, 8) selection of BTcP medication, 9) dosing BTcP medications, and 10) education. These steps may help clinicians to recognize and treat BTcP adequately.

Keywords: breakthrough cancer pain, cancer pain, opioids.

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Introduction

The term “breakthrough cancer pain” (BTcP) was introduced about 25 years ago [1]. This pioneer study suggested that there is a temporal variability in pain intensity with peaks interrupting a state of adequate analgesia. At that time, the variability of pain had already been considered because some tools designed for pain assessment tried to explore this condition by measuring pain at its “worst,” “least,” “average,” and “now” [2,3]. This concept has changed the way of managing cancer pain. Patients with cancer pain were traditionally treated with oral opioids, namely, immediate-release morphine at regular intervals (every 4 hours), providing the same dose when the pain got severe [4], particularly during opioid dose titration, until achieving an adequate analgesia. It was implicit that the same dose could be given every time the pain worsened. Doses were then increased on the basis of the average or worst pain. This approach was frequently associated with the prevalence of central adverse effects. Portenoy et al. [1,5] suggested that pain could be adequately controlled for most hours of the day with analgesics given at regular intervals, whereas the peaks of pain intensity could be separately treated with other therapeutic options providing fast and short analgesia. These peaks of pain intensity reported in patients with cancer had been invariably examined in the past years, providing relevant information for a better knowledge of this phenomenon and its treatment. The aim of this critical review was to provide the golden rules, namely, the 10 commandments, for a correct diagnostic pathway of BTcP and a consequent personalized pharmacological treatment. Table 1

First Commandment: Background Analgesia

Background analgesia should be carefully assessed. Studies have invariably considered BTcP as a transitory increase in pain to greater than moderate intensity that occurs on a baseline pain of moderate intensity or less. This definition, however, could be ambiguous because background pain and BTcP may overlap and then cannot be easily distinguished. Moderate pain is often worthwhile of treatment or therapeutic refinements because of its interference with most quality-of-life issues [6]. Indeed, most epidemiological surveys did not provide a definition a priori, and so a large variability has been reported for this phenomenon [7]. Literature has reported several surveys in which BTcP was analyzed in patients who did not have an appropriate background analgesia, that is, the preliminary criterion for a diagnosis of BTcP. Patients were undertreated or had insufficient analgesia. Indeed, optimization of background pain is mandatory before taking BTcP into consideration [8]. End-of-dose failure, initially constituting a subtype of BTcP [1], is no longer considered as

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such, but is rather a form of uncontrolled pain requiring some adjustment of opioid therapy [9,10]. Thus, before considering BTcP, the intensity of background pain should be mild for most hours of the day and most efforts should be dedicated to optimize basal pain control [8,9,11].

Second Commandment: Drugs Used for Background Analgesia
In the subsequent years a more meaningful definition of BTcP was proposed, which included the introduction of a second variable—the use of stable doses of opioids that are able to maintain baseline pain control [5,12]. In many studies, the use of nonopioids or opioids for moderate pain for background analgesia resulting in poor pain control has dramatically confounded the epidemiological picture of this phenomenon [13–20]. It is likely that BTcP should be more correctly defined as an episode of severe pain intensity in patients receiving an adequate treatment with opioids that are able to provide at least mild background analgesia [9–11].

Third Commandment: Breakthrough Pain Exists!
Different BTcP prevalence rates, ranging from 30% to 90%, have been reported in literature. As mentioned earlier, many epidemiological studies did not provide a definition a priori, and so in a recent review a large variability has been reported for this phenomenon, in which articles were mixed without considering the minimal data set to describe BTcP [7]. According to the first two commandments, differences in the evaluation of baseline pain and BTcP episodes and the use of nonopioid analgesics have dramatically confounded the epidemiological data [13–20]. Nevertheless, the phenomenon exists and involves three-fourth of patients, even when receiving optimized opioid therapy that provides mild background analgesia [9]. Some studies have shown that the prevalence and characteristics of BTcP may change through the course of disease [21,22]. In patients with advanced cancer with a lower performance status, the prevalence of BTcP could be lower, possibly because of a reduced incident pain component, given the limited physical activity [23].

Fourth Commandment: Characteristics of BTcP
Several studies have shown that BTcP is not a unique entity, but a heterogeneous condition because episodes vary between individuals and also within individuals. Two large subclasses have been identified. Spontaneous-type BTcP, often named idiopathic, is when BTcP occurs with no identifiable cause or precipitant event. Generally, the onset and duration of this BTcP subtype may be longer [23,24]. Predictable incident-type pain is when BTcP is triggered by an identifiable event, typically the movement in patients with bone metastases or swallowing in patients with oral mucositis. The onset of this subtype of BTcP is rapid and the duration is shorter [23,24]. In general, three to four episodes per day have been considered acceptable when most hours of the day are covered by an adequate pain relief [5]. Nevertheless, the modalities of BTcP development may be different even in these subcategories. There are some typical episodes that are triggered by several factors, for example, incident pain due to bone metastases, which can occur more frequently. Most of these BTcP episodes are elicited by physical activity in the presence of bone metastases. Stopping the physical activity or the movement inducing pain may spontaneously subside the episode. In some cases, pain develops every time the patient tries to move and is potentially self-limited because it often depends on the will of maintaining an activity or resting. In other cases, this kind of pain can persist, lasting even after the patient stops the activity. This status corresponds to a relevant interference with daily living because patients may prefer to limit their activity to avoid triggering BTcP or use individual strategies in their daily life to prevent the occurrence of BTcP.

Thus, the focus of the treatment should be to find a compromise between activity and background analgesia. It is of interest that in a subclass of patients with abdominal disease, it has been estimated that about 55% of the patients with well-controlled background pain will develop BTcP episodes. This percentage was estimated to be higher (about 90%) in patients who presented with uncontrolled background pain, underlying the need to better characterize patients with BTcP only after a careful optimization of basal pain, as considered by the definition of BTcP [25].

The characteristics of BTcP can change during the course of disease. Patients with advanced cancer in a setting of palliative care were older, had lower Karnofsky levels, a lower number of BTcP episodes per day, a slower onset of BTcP, and a less predictable BTcP than did patients assessed in a pain clinic or an oncological ward [21–23].

Fifth Commandment: Making a Diagnosis, the Loop of Commandments 1 to 4
It is difficult to have a clear idea of a complex phenomenon without a prospective evaluation and an optimized analgesic approach for baseline pain. Thus, it is likely that BTcP be more correctly defined, according to the previous commandments, as an episode of severe pain intensity in patients receiving an adequate treatment with opioids that are able to provide at least mild analgesia [9–11]. A clear distinction between levels of pain intensity commonly considered to be acceptable (≤ 4 on a numerical scale of 0–10) and BTcP, which is a severe episodic pain (≥ 7 on a numerical scale of 0–10), is needed. It has recently been found that in patients with baseline pain of mild intensity (≤ 4 on a numerical scale of 0–10), the meaningful pain intensity for asking for a BTcP medication was about 7 or more [9,11]. Although there might be variations in individuals, these levels of pain intensity are widely used for defining mild pain (≤ 4 on a numerical scale of 0–10) and severe pain (≥ 7 on a numerical scale of 0–10) [6]. This aspect has obvious implications from both the epidemiological and the therapeutic points of view.

Sixth Commandment: Assessment
A specific assessment should be performed in individuals to provide further information for a specific treatment. Several tools to assess patients’ experience of BTcP have been proposed, but only a minority have been partially validated [26]. Some questionnaires have been developed to assess BTcP. A Delphi instrument was developed, followed by patient pretesting on the clarity and feasibility of completing the instrument, and submitted to a panel of national and international experts to provide indications to screen BTcP, attempting to group the principal items commonly used in the clinical setting. Key issues included the relationship with baseline pain, the last time when BTcP was experienced, frequency, intensity of pain at peak, location, quality, time from onset to peak intensity, duration, causes, predictability, general relief, relief from BTcP medication, satisfaction with BTcP medication, onset of pain relief, and satisfaction with onset of pain relief. Other items completed by professionals included etiology of BTcP and inferred pathophysiology of BTcP [27]. More recently, a new assessment tool for BTcP has been developed. This instrument provides information on how BTcP and the efficacy and toxicity of BTcP medications may
interfere with daily life. Reliability and validity of the tool tested on a group of patients was reasonably good [28].

The number of episodes considered to be acceptable has been invariably reported as being one to four episodes per day. This concept, however, is not extensible to all types of BTcP. For example, incident bone pain due to movement represents a unique category of BTcP because pain is induced by activity, and the number of episodes is difficult to account because the patient will try to avoid painful maneuvers, strongly limiting his or her quality of life. In some circumstances, every movement induces pain of variable duration, depending on the will of the patients in stopping the activity. In this case, more attention should be paid to optimization of background opioid analgesia, to allow to find a compromise between an acceptable mobilization and the level of opioid adverse effects at rest [8]. As reported earlier, patients with advanced cancer with a low performance level or bedridden patients will develop BTcP less frequently [21–23] for a lesser physical activity. Accordingly, characteristics may change and may require a different management. Thus, reassessment should be frequently performed during the course of disease. Monitoring of the use of these products is mandatory to diagnose a change in the clinical picture, suggesting a revision of background analgesia, or to reveal suspect attitudes, suggesting drug abuse.

**Seventh Commandment: Tailored Pharmacological Treatment of BTcP**

As BTcP presentations may differ in individuals, strategies should be chosen case by case, tailoring the treatment. When BTcP is predictable, for example, before starting a physical activity, a preemptive analgesia, which is giving an analgesic before the predictable event inducing pain, could be indicated. Oral opioids in the immediate-release formulation, such as morphine, could be administered 30 minutes before starting an activity because they produce a clinical analgesic effect in 30 to 45 minutes. This strategy, however, requires a good patients’ collaboration because it needs some training and good compliance for timing of administration in relation to the onset and duration of BTcP. Oral morphine could also be a good option when a predictable episode develops slowly after starting an activity.

The principal characteristic of BTcP is its temporal pattern and most BTcP episodes peak in intensity within a few minutes and last for 30 to 60 minutes [22,24]. Thus, a rapid intervention with fast-onset analgesics is necessary. Fentanyl is a potent and strongly lipophilic drug that matches the characteristics to favor the passage through the mucosa and then across the blood-brain barrier to provide fast analgesia. Different technologies have been developed to provide fast pain relief with fentanyl, delivered by noninvasive routes [29]. Generations of transmucosal preparations of fentanyl, each with its particularities and availabilities, have been introduced in the market in the last decade. These products provide a rapid effect clinically observable 10 to 15 minutes after drug administration and are more effective than placebo and oral opioids [30–40]. Because these products have been tested in opioid-tolerant patients, all the studies performed with fentanyl products have recommended that these drugs should be administered to tolerant patients, receiving doses of oral morphine equivalents of at least 60 mg [29]. Despite the relevant evidence in favor of fentanyl products, the guidelines of the National Institute for Health and Care Excellence suggested that morphine is the first-choice drug for BTcP [41]. This statement was based on the doubtful advantages of fentanyl expected after 30 to 60 minutes and possibly on the expensiveness of the new drugs. The temporal pattern of fentanyl products, however, is designed to provide an analgesic effect within 5 to 15 minutes, rather than when most episodes may disappear spontaneously (30-60 minutes), as it occurs with oral morphine. Pharmacokinetic studies do not support an early analgesic effect of oral morphine able to overlap the temporal pattern of most episodes of BTcP because a clinical effect, based on its pharmacokinetics, is expected after 30 to 45 minutes [42]. It is of interest that the use of morphine is just anecdotal and no evidence has been provided for its use in BTcP management. No study has ever assessed the efficacy of oral morphine for BTcP as primary outcome.

**Eighth Commandment: Does the Best Fentanyl Product Exist?**

Comparative studies of fentanyl products are poor, and the choice of fentanyl products is still a matter of controversy. It is clear that the molecule is always the same, and so there are differences regarding the clinical application of different delivery systems. These products have different pharmacokinetic profiles and availabilities that may make the difference in individual clinical situations. Few comparison studies are available. In an open-label, crossover trial, intranasal fentanyl spray (INFS) was compared with oral transmucosal fentanyl citrate (OTFC). The time to onset of meaningful pain relief was shorter with INFS, and pain intensity differences were significantly greater for INFS than for OTFC from 5 minutes postdosing, with a higher number of patients achieving a pain intensity reduction at 5 minutes and 10 minutes. Finally, more patients preferred INFS than OTFC. No serious adverse effects were attributed to study medications [43]. More recently, a comparison of nasal products administered in doses proportional to the basal opioid regimen was performed. Both delivery systems, when using fentanyl doses proportional to the basal opioid regimen, provided similar analgesia within 5 to 10 minutes, achieving a mean decrease in pain intensity of more than 50% 20 minutes after administration [44].

Data regarding some practical aspects of administering BTcP medications have been rarely examined. Fentanyl buccal tablet (FBT), sublingual fentanyl (SLF), and INFS given as placebo have been assessed in addition to the usual rescue analgesic used for BTcP. For accessibility, the usual rescue analgesic was rated mildly easy and significantly better than FBT and INFS, but not SLF. For ease of administration, the usual rescue analgesic and SLF were similar, and SLF was rated better than FBT and INFS. SLF was also rated the best for palatability and overall impression. It was, however, unclear what the usual rescue analgesic was and only three fentanyl products were evaluated in the form of placebo [45]. In a recent report assessing the acceptability of rapid-onset opioids for BTcP in patients with advanced cancer, all fentanyl products were well accepted, with OTFC being significantly considered to be more problematic for its modality of administration and late pain relief in comparison with other products. Thus, the second generation of fentanyl delivery systems seems to have more favorable characteristics for some practical issues [46]. OTFC, formulated as self-administration of a solid drug matrix on a handle, requires more patient discipline and focus, which may limit compliance, particularly in patients with weakness, a common symptom in the advanced stage of the disease. From a clinical perspective, the choice of transmucosal fentanyl preparation depends on the status of mucosa. Thus, the assessment of oral and nasal mucosal surfaces is mandatory. In patients with oral problems, for example, due to mucositis, dry mouth, or infection, the use of oral transmucosal products may be of concern, and so nasal products should be preferred. Nevertheless, patients with rhinitis or nasal lesions are not candidates for nasal administration. Periodical assessment of clinical conditions capable of interfering with the bioavailability of the drugs and their effectiveness is useful in providing the continuous efficacy of fentanyl delivery systems. At the end of the day, fentanyl products should be chosen according to different clinical and practical
conditions considering their indications, ability to use the delivery system, and mucosal conditions due to oncological-radiotherapy treatment, which may impede good absorption. Finally, not all the products are often available at the level of the local health care systems or regionally, and reimbursement modalities may differ among countries Table 1 [47].

### Ninth Commandment: Dosing BTcP Medications

There is a consolidated tradition of using oral opioids, such as morphine, in doses proportional to basal opioid regimen. Nevertheless, pioneer studies of fentanyl products provided unexpected data; that is, the effective dose was not related to the basal opioid regimen. As a consequence, the doses of fentanyl products should be titrated for each patient starting with the lowest strength. This observation has been labeled as a statement on the basis of evidence [10]. Several flaws, however, led to this interpretation. This is in contrast to the scientific knowledge, given that opioid-tolerant patients receiving high doses of opioids are expected to require a dose proportional to the background opioid regimen to provide a clinical analgesic effect [48–50]. As mentioned earlier, oral morphine has been safely given for dozens of years in doses proportional to the opioid basal regimen, even doubling the nightly dose, suggesting that fentanyl products can also be used in such clinical practice, the titration process provided doses even higher than those expected by using doses proportional to basal opioid regimen [63]. Thus, it is likely that patients receiving high doses of opioids for background analgesia are highly tolerant and could have poor analgesia with the first phase of dose titration, contributing to a frustrating attempt not followed by an appropriate analgesic effect.

<table>
<thead>
<tr>
<th>Opioid</th>
<th>$T_{\text{max}}$ (min)</th>
<th>Dissolution time (min)</th>
<th>Availability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTFC</td>
<td>20–40</td>
<td>15</td>
<td>50</td>
</tr>
<tr>
<td>FBT</td>
<td>45–96</td>
<td>15</td>
<td>65</td>
</tr>
<tr>
<td>SLF</td>
<td>40–57</td>
<td>2</td>
<td>70</td>
</tr>
<tr>
<td>FBSF</td>
<td>60–120</td>
<td>–</td>
<td>65</td>
</tr>
<tr>
<td>INFNS</td>
<td>13–23</td>
<td>–</td>
<td>80–90</td>
</tr>
<tr>
<td>FPNS</td>
<td>15–21</td>
<td>–</td>
<td>70</td>
</tr>
</tbody>
</table>

Note. Results are from various studies using different doses and methodologies and are not comparable. BTcP, breakthrough cancer pain; FBSF, fentanyl buccal soluble film; FBT, fentanyl buccal tablet; FPNS, fentanyl pectin nasal spray; INFNS, intranasal fentanyl spray; OTFC, oral transmucosal fentanyl citrate; SLF, sublingual fentanyl.

* Percentage of daily doses.

### Tenth Commandment: Education

Most patients receiving opioids for cancer pain will need a double prescription, also including a BTcP option. Regardless of the individual indication found after a careful assessment of the clinical condition, it is of paramount importance to consider patients’ and relatives’ education to maximize the effects of the drug prescribed for BTcP.

A relevant aspect is represented by a patient’s experience and compliance. A balance between the individual indications and the patient’s will, preference, and ability to use the product is fundamental to find an acceptable compromise between the clinical need and the individual attitudes and to plan an appropriate prescription to be correctly followed by patients and relatives. Time should be usefully spent to explain to patients how to use BTcP medications according to the delivery system and how often it should be allowed. Before prescribing a drug, patients should be informed about the local availability in the pharmacies. Patients should also be informed to contact the physician when the number of episodes increases in time or the dose of BTcP medication is no longer efficacious. This may correspond to the loss of pain control, which requires a reassessment of the clinical situation and a change in pain therapy.

### References


