

## Breakthrough Pain in Cancer Patients— Pharmacologic Symptomatic Treatment

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### Abstract

Breakthrough pain is experienced by many cancer patients who are being treated with opioids for the management of chronic persistent pain. There is currently no 'gold standard' approach for the pharmacologic symptomatic treatment of breakthrough pain but proposed strategies include the implementation of primary therapies (e.g. chemotherapy, radiotherapy, and surgery) for the underlying cause of the pain; optimization of scheduled analgesia; use of adjuvants; and specific supplemental analgesia for breakthrough pain (the most common pharmacologic strategy). Individualization of treatment is important and a combination of these strategies may be required. In this article, pharmacotherapeutic approaches to managing breakthrough pain are discussed, including different routes of administration and newer opioid formulations. In addition, the current guidelines for managing breakthrough pain are examined.

### Keywords

Breakthrough pain, cancer, opioid, supplemental analgesia, background pain, quality of life

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Breakthrough pain is a transitory flare of pain superimposed on an otherwise stable pain pattern in patients treated with opioids.<sup>1</sup> Breakthrough pain is a common feature in patients with cancer and is associated with significant physical, psychologic and economic burdens on patients as well as their care-givers.<sup>2</sup> The most common subtype of breakthrough pain is incident pain, which is due to movement and is commonly associated with bone metastases or fractures.<sup>2</sup> Breakthrough pain can also be idiopathic and occur spontaneously, with no obvious precipitating event. Another type of breakthrough pain is the incident non-predictive pain that is precipitated by non-volitional factors (e.g. bladder spasm or coughing).<sup>2</sup>

The successful management of breakthrough pain may involve a number of different interventions. For some patients, optimization of around-the-clock (ATC) analgesia according to the World Health Organization (WHO) analgesic ladder will suffice in managing breakthrough pain. For the majority of patients, however, other avenues of pharmacotherapeutic treatments for breakthrough pain are needed. These include supplemental doses of analgesics, the most common pharmacologic treatment strategy for managing breakthrough pain. The goal of pharmacologic treatment of breakthrough pain is ultimately to

reduce the intensity and frequency of pain episodes. In the current article, the pharmacotherapeutic approaches available for managing episodes of breakthrough pain will be discussed, focusing on the various opioid formulations and administration routes.

### Optimization of Around-the-clock Analgesia

In order to manage breakthrough pain, background pain should be effectively managed and controlled by ATC analgesics.<sup>3</sup> The effectiveness of ATC treatment for background pain should be regularly assessed, with reassessment advised if breakthrough cancer pain incidence occurs more than four times per day.<sup>4</sup> Optimizing the ATC analgesia according to the principles of the WHO analgesic ladder may help ameliorate breakthrough pain.<sup>5</sup> According to the WHO ladder, a first step can be the oral administration of acetaminophen and/or non-steroidal anti-inflammatory drugs (NSAIDs). This is appropriate assuming that the pain is of mild intensity (4 or less on the 0–10 numeric rating scale) and there are no contraindications for organ toxicity or tolerability issues related to the use of such drugs. Studies have shown that effective management of background pain is possible with the use of NSAIDs,<sup>6</sup> although there is no specific evidence in breakthrough pain.

If pain is not adequately reduced, in the absence of treatment-limiting side-effects an increase in the ATC opioid dose may be considered in an effort to reduce the frequency or intensity of breakthrough pain. Examples of potent opioid agonists used for managing background pain include:

- transdermal fentanyl;
- controlled-release oxycodone;
- extended-release hydromorphone;
- methadone, morphine (controlled-, sustained- and extended-release formulations); and
- extended-release oxymorphone.

These drugs are characterized by a slow onset of action and their pharmacokinetic profiles have minimal peaks and troughs that result in stable blood levels over the dose period.<sup>7</sup> Studies have shown that increasing the ATC opioid medication may result in improved background and breakthrough pain.<sup>8,9</sup> Even though these studies are on a small scale, optimization of ATC opioid dose is a potential strategy for managing breakthrough pain, with the opioid dose being lowered again if the patient experiences adverse effects between episodes of breakthrough pain.<sup>10</sup>

### Adjuvant Analgesics

In addition to these steps, the use of adjuvant drugs can be considered at all stages of the patient's illness and at each step of the WHO analgesic ladder.<sup>11</sup> Adjuvant analgesics are a diverse group of drugs that were originally developed for a primary indication other than pain. Many of these medications are currently used to enhance analgesia under specific circumstances. Of interest, a few of these agents are currently used as primary analgesics for specific pain conditions as well as adjuvants in some other pain conditions.<sup>12</sup> Adjuvant analgesics (e.g. antidepressants, anticonvulsants, N-methyl-D-aspartic acid antagonists, corticosteroids, and topicals) can be administered alone, but they are usually accompanied by acetaminophen/NSAIDs and opioids.<sup>11</sup> Adjuvant analgesics are widely used, especially for the relief of neuropathic cancer pain, which can present with a component of breakthrough pain.<sup>13,14</sup>

### Supplemental Analgesia

The use of supplemental doses of analgesics is the cornerstone of pharmacologic treatment strategies for managing breakthrough pain. This type of medication is taken as required, rather than on a regular basis. The ideal supplementary analgesic should be efficacious, with a rapid onset, relatively short duration of action, and minimal adverse effects. It can be used either prophylactically, for predictable volitional incident pains or procedural pains, or at the onset of breakthrough pain for unpredictable spontaneous pain or non-volitional incident pains.<sup>2</sup>

Non-opioid analgesics and adjuvant analgesics have been used/ investigated as supplemental medication for episodes of breakthrough pain, but they typically have a slow onset and relatively long duration of action.<sup>15-17</sup> For this reason, in the majority of cases the most appropriate supplemental medication will be an opioid analgesic.

The most common method of providing supplemental medication is with oral short-acting formulations of morphine and other opioid analgesics.

Despite their short-acting nature, the pharmacokinetic/pharmacodynamic profiles of these oral opioids (onset of action: 30–40 minutes; duration of effect: about four hours) do not tend to mirror the temporal characteristics of most breakthrough pain episodes.<sup>4</sup> For this reason, these oral opioid formulations are most effective for predictable incident breakthrough pain, for which they can be given 30–45 minutes before a known triggering activity. Efforts to deliver rescue medication more effectively have explored alternatives to the oral route, including parenteral, rectal, inhaled, intranasal, sublingual, and oral transmucosal preparations.

### Parenteral Opioids

The parenteral routes of opioid administration (intravenous and subcutaneous) have been shown to be effective, well tolerated, and safe for the management of breakthrough pain.<sup>18,19</sup>

The use of parenteral opioids is, however, associated with several disadvantages. For example, any indwelling intravenous catheter can become a site of infection and thus requires skilled nursing attention if the patient is unable to care for catheter access.<sup>20</sup> In addition to this, more costs are involved as this route requires preparation of the opioid solution for injection by the pharmacist and administration of the infusion via an external pump.<sup>20</sup> Despite this, the rapid onset of action associated with this route of administration means that it may be acceptable in cases where the breakthrough pain is severe.<sup>21</sup>

### Oral Transmucosal Opioids

The oral transmucosal routes of administration (buccal and sublingual) have increasingly been used in the management of breakthrough pain episodes.<sup>22</sup> The mouth provides a large mucosal surface for drug absorption, allowing drugs to enter the systemic circulation directly, bypassing the gastrointestinal tract and first-pass metabolism in the liver.

Fentanyl citrate, a synthetic opioid, has a rapid onset of effect and a short duration of action,<sup>23</sup> matching the temporal characteristics of a breakthrough pain episode. Furthermore, its high lipophilicity makes a number of routes of administration feasible, including oral transmucosal. The US and European approval of oral transmucosal fentanyl citrate (OTFC), a lozenge impregnated with fentanyl designed to dissolve slowly in the mouth, was an important advance in breakthrough pain treatment. It provides a non-invasive method of administration and has demonstrated a faster onset of relief and greater degree of breakthrough pain relief than oral morphine.<sup>24,25</sup> In addition, a Cochrane review confirmed the effectiveness of this modality for treating breakthrough pain and reported that OTFC produced faster/greater analgesia than oral morphine.<sup>22</sup>

A second oral transmucosal product with marketing authorization in the US and Europe is the effervescent buccal fentanyl tablet.<sup>26</sup> This tablet provides rapid penetration of fentanyl through the buccal mucosa by using effervescence to cause pH shifts that enhance the rate and extent of fentanyl absorption. The efficacy of this formulation has been shown in placebo-controlled studies that demonstrated an analgesia onset that was faster than would be expected from oral therapy.<sup>27-30</sup>

Mucoadhesive film formulations of fentanyl for buccal or sublingual absorption aimed at rapid relief from breakthrough pain are also

available. Fentanyl buccal soluble film (FBSF) is a transmucosal delivery system based on a polymer film. It delivers fentanyl across the mucosa in a pH-dependent manner.<sup>31</sup> FBSF was shown to be efficacious and safe in a placebo-controlled study of breakthrough pain patients<sup>32</sup> and has recently been approved in this setting in the US, Canada, and Europe.

A sublingual tablet formulation of fentanyl that uses mucoadhesives to hold the fentanyl in contact with the mucosa has also been marketed in Europe and has recently received Food and Drug Administration (FDA) approval in the US. Sublingual fentanyl citrate comes as a rapidly disintegrating tablet consisting of an ordered mixture of fentanyl combined with soluble carrier particles that is rapidly absorbed.<sup>33</sup> This formulation was tested in a randomized, placebo-controlled phase III trial in opioid-tolerant patients with breakthrough cancer pain. Here, sublingual fentanyl citrate provided significant improvements in pain intensity compared with placebo from 10 minutes post-administration. It was well-tolerated both systemically and sublingually.<sup>34</sup>

### Intranasal Opioids

The intranasal route is another option for achieving rapid uptake of opioids. It is currently being used/investigated to provide acute and breakthrough pain relief. The large absorptive surface area of the nasal mucosa is highly vascular and thus offers rapid absorption of drugs into the systemic circulation while bypassing gastrointestinal and hepatic pre-systemic metabolism.<sup>35</sup> This route of administration may be more acceptable to patients who experience nausea, vomiting, oral mucositis, impaired gastrointestinal function, and xerostomia, for whom the oral route of administration may be difficult.

A potential disadvantage with the intranasal route is the relatively small volume of drug the nose is able to accommodate. The efficacy of intranasal fentanyl spray (INFS) was compared with that of OTFC for the relief of cancer-related breakthrough pain in an open-label trial.<sup>36</sup> The difference in pain intensity was significantly greater for the INFS than OTFC from five minutes post-dosing. Clinically important pain relief ( $\geq 33\%$  reduction in pain intensity) was seen five minutes after INFS treatment in a quarter of breakthrough pain episodes.

A second intranasal fentanyl formulation, fentanyl pectin nasal spray provided rapid analgesia and clinically meaningful pain relief ( $\geq 2$  point decrease in pain intensity on a 0–10 numerical scale) versus placebo in a randomized, double-blind study in breakthrough cancer pain patients.<sup>37</sup> INFS and fentanyl pectin nasal spray were well-tolerated and patient acceptability of the intranasal formulations was high in both studies.<sup>36,37</sup>

Both INFS and OTFC are approved in Europe for the management of breakthrough pain. Other fentanyl formulations and devices for intranasal administration are currently being developed. These include an intranasal formulation of the fentanyl analog sufentanil, which was shown to be safe and effective in a prospective, open-label study of patients with cancer-related breakthrough pain.<sup>38</sup>

### Inhaled Opioids

The lungs present a large surface area for drug absorption but there are limited data investigating the use of inhaled opioids in patients with breakthrough pain. This may be because the route has a number of

limitations. It requires complex devices to create a mist prior to inhalation, as well as various types of nebulizers (depending on the patient).<sup>39</sup>

### Rectal Opioids

Rectal administration of opioids offers the possible pharmacokinetic advantage of directly entering the systemic circulation via the lower rectal veins. It is also useful for patients who are unable to tolerate oral or parenteral routes due to bleeding disorders or generalized edema.<sup>40</sup>

Several types of rectal opioid preparations may be formulated, depending on the country and the acceptance of patients and care givers. In the US, compounding pharmacies can prepare opioid (e.g. hydromorphone) suppositories. The administered dose is usually the same as the oral dose.

Even though rectal administration can provide rapid pain relief, absorption rates are variable, and therefore the amount of pain relief can also vary for the doses administered.<sup>41</sup> In a study of 100 patients with chronic cancer-related pain, patients were asked to complete a questionnaire concerning the acceptability of nine administration routes. The rectal route was the least acceptable.<sup>21</sup>

The decision to use a specific opioid preparation should be based on a combination of:

- the pain characteristics (onset and duration);
- the product characteristics (pharmacokinetics and pharmacodynamics);
- the patient's previous response to opioids (efficacy and tolerability); and particularly
- the patient's preference for an individual preparation.

### Dosing of Supplemental Opioid Analgesia

Traditionally, based largely on anecdotal experience, it has been advised that a supplemental opioid dose roughly equivalent to 5–10% of the total opioid background medication dose should be administered as needed every two to four hours.<sup>1</sup> The European Association for Palliative Care (EAPC) guidelines on morphine use in cancer pain recommend the use of the equivalent of a four-hourly dose (approximately 16% of the daily dose) of usual opioid to control breakthrough cancer pain.<sup>22,42</sup> Studies investigating various supplemental opioid formulations have, however, suggested the absence of a relationship between the effective dose of these preparations and the fixed ATC opioid dose.<sup>24,27,28,30,37</sup> The current recommendation is therefore that each patient is titrated to a successful dose of supplemental opioid that produces adequate analgesia and minimal adverse effects.<sup>43</sup> The need to titrate transmucosal opioid doses is the subject of much debate. For example, OTFC given in doses proportional to the basal opioid regimen has been found to be quite effective and, above all, safe in treating breakthrough pain.<sup>22,44</sup> Further clinical studies are necessary to examine this issue.

### Recommendations for the Management of Breakthrough Pain

According to the EAPC, a number of factors—such as class of drug, route of administration, dosage, patient setting, and breakthrough pain subtype—should be taken into account when selecting the appropriate medication.<sup>45</sup> The National Pain Education Council suggest that when

**Table 1: Recommendations for the Management of Cancer-related Breakthrough Pain from the Task Group of the Science Committee of the Association for Palliative Medicine (UK and Ireland)**

Recommendations
Patients with pain should be assessed for the presence of breakthrough pain
Patients with breakthrough pain should have this pain specifically assessed
The management of breakthrough pain should be individualized
Consideration should be given to the treatment of the underlying cause of the pain
Consideration should be given to the avoidance/treatment of the precipitating factors of the pain
Consideration should be given to modification of the background analgesic regimen/around the clock medication
Opioids are the 'rescue medication' of choice in the management of breakthrough pain episodes
The dose of opioid 'rescue medication' should be determined by individual titration
Non-pharmacologic methods may be useful in the management of breakthrough pain episodes
Non-opioid analgesics may be useful in the management of breakthrough pain episodes
Interventional techniques may be useful in the management of breakthrough pain
Patients with breakthrough pain should have this pain specifically re-assessed

prescribing a drug for breakthrough pain, the 'Four As' of pain treatment should be considered:<sup>46</sup>

- analgesia;
- activities of daily living;
- adverse events; and
- aberrant drug-taking behaviors.

In addition, a task group of the UK and Ireland Association for Palliative Medicine made a series of 12 recommendations about certain generic strategies to manage breakthrough pain (see *Table 1*).<sup>47</sup> A key point emphasized by this group was that the successful management of breakthrough pain depends on adequate reassessment of the patient, the objective of which is to determine the efficacy and tolerability of the treatment and any change in the nature of the breakthrough pain. Inadequate reassessment may lead to the continuance of ineffective and/or inappropriate treatment.<sup>47</sup> In the absence of a validated clinical breakthrough pain assessment tool, the group recommended the use of standard pain scales to determine the response to treatment (e.g. verbal and numerical rating scales), the choice of which should be made on an individual basis.

## Current Status and Future Challenges

Although the effective treatment of background and breakthrough cancer pain is a major goal for physicians involved with pain management, the possible aberrant use of opioids is a concern. There is a fear of drug misuse or abuse in:

- vulnerable patients with positive risk factors or a past history of addiction; and
- in the subpopulation of patients affected by both drug addiction and

cancer pain, especially when immediate-release and rapid-onset opioid formulations are used.

Therefore, many chronic pain patients can be left undertreated, resulting in unrelieved pain and diminished quality of life.<sup>48</sup> It is known that patients with a history of drug abuse and psychiatric illness are more likely to abuse opioid medication.<sup>49</sup> The opioid risk tool and the screener and opioid assessment for patients with pain are examples of tools in the form of brief, self-administered written surveys. These can predict the level of risk for developing aberrant drug-related opioid use behaviors in patients.<sup>50,51</sup>

It has been suggested that all patients that are treated with opioids should be monitored in order to identify and manage opioid abuse. Moreover, higher-risk patients should be watched more closely and have monitored prescriptions so that appropriate pain relief is provided while aberrant drug-related behavior is prevented.<sup>52</sup>

A practical approach recommended for monitoring opioid use involves having the patient agree that opioids will be prescribed by a single provider and supplied by a single pharmacy.<sup>53</sup> An additional suggestion is that a limited drug supply be offered to the patient, with limited refill opportunities (e.g. in the case of theft). Higher risk patients should be required to make more frequent visits for prescriptions and other important monitoring tools can be scheduled, such as random urine toxicology screening and pill counts.<sup>54</sup>

Opioid drugs, when used properly, can be beneficial as tools for the management of persistent or breakthrough pain. Steps taken by the US Food and Drug Administration (FDA) and drug manufacturers include the provision of additional warnings in product labeling, implementing risk management plans, conducting inter-agency collaborations and the issuing of direct communications to both prescribers and patients. The FDA has proposed a risk evaluation and mitigation strategy (REMS) for opioids with the aim of minimizing the risks associated with opioid use while ensuring that patients who need these drugs continue to have appropriate access.<sup>55</sup> As part of this strategy, in February 2009 the manufacturers of certain opioid pain medications, most of them extended-release products or transdermal systems, were informed that these agents would be required to have a REMS. This includes a restricted distribution program under which prescribers, pharmacies, and patients would have to register in order to prescribe, dispense, and receive this opioid, respectively.

Later in the same year, the FDA approved the first opioid with an associated REMS program: FBSF. As part of the FBSF REMS, this dosage form will only be available through a restricted distribution program called the FOCUS program.<sup>56</sup> The development of REMS for extended-release opioid products is still the subject of much discussion and consultation between the FDA, industry, and other stakeholder groups.

## Conclusion

Breakthrough pain is a heterogeneous condition and its management may involve a number of different interventions, including opioids, which have traditionally played an important role in breakthrough pain management. In some cases, optimizing ATC opioids may be helpful;

however, the most common strategy is to deliver supplemental analgesia either prophylactically for predictable pain or as soon as pain starts if unpredictable.

It is clear that fast-acting opioid formulations and improved administration routes will continue to play an important role in managing breakthrough

cancer pain. In particular, new formulations of fentanyl and improved delivery mechanisms hold great promise for improving quality of life for the majority of cancer patients living with the burden of breakthrough pain. The doses to be administered are still a matter of controversy in the literature and additional studies with specific designs should be conducted to settle the question. ■

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