Breakthrough cancer pain (BTP) is common and can have a significant impact on the quality of life of cancer patients. Because it is heterogeneous, management needs to be individualised to achieve the best pain management for each patient. This review is a summary of a Menarini-sponsored educational meeting on BTP presented by Dr Andrew Davies from the Royal Surrey County Hospital, United Kingdom. Dr Davies’ presentation included how supportive care fits in with palliative care, clinical features of BTP, the Association of Palliative Medicine (APM) recommendations for the treatment of BTP, the use of rapid onset opioids, and some of the ongoing controversies such as addiction and abuse.

**Breakthrough pain**

The first step in the effective management of breakthrough cancer pain (BTP) is understanding what it is and what it is not. Breakthrough pain is not the same as exacerbation pain, opioid titration pain or end of dose pain. In 2008 a task group of the Association of Palliative Medicine (APM) was convened to produce evidence-based clinical guidelines on the management of cancer-related breakthrough pain based on the scientific literature. The group defined breakthrough pain as “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”.

Several definitions of BTP have since been proposed, and all definitions have the common feature of “controlled” background pain. The APM definition is still used in clinical practice, as evident by the results of a recent survey that showed the APM definition had the highest level of agreement among Specialists.

**Recommendations for the diagnosis and management of BTP**

Based on the available evidence, the APM made 12 recommendations for the diagnosis and management of BTP. Each recommendation was graded from A to D based on the quality of the evidence. Because there was very limited randomised controlled trial data (Grade A) available at the time the guidelines were created, most of the recommendations were based on limited evidence such as case studies and expert opinions (Grade D), except for recommendation 8 which was graded with a B.

The 12 recommendations were:

1. Patients with pain should be assessed for the presence of breakthrough pain (grade of recommendation: D)
2. Patients with breakthrough pain should have this pain specifically assessed (D)
3. The management of breakthrough pain should be individualised (D)
4. Consideration should be given to treatment of the underlying cause of the pain (D)
5. Consideration should be given to avoidance/treatment of the precipitating factors of the pain (D)
6. Consideration should be given to modification of the background analgesic regimen/“around the clock” medication (D)
7. Opioids are the “rescue medication” of choice in the management of breakthrough pain episodes (D)
8. The dose of opioid “rescue medication” should be determined by individual titration (B)
9. Non-opioid analgesics may be useful in the management of breakthrough pain episodes (D)
10. Non-pharmacological methods may be useful in the management of breakthrough pain episodes (D)
11. Interventional techniques may be useful in the management of breakthrough pain (D)
12. Patients with breakthrough pain should have this pain specifically reassessed (D).

**Diagnosis of BTP**

When recognising and diagnosing BTP, it is important to realise that it can only occur if the background pain is well controlled. The APM algorithm for the diagnosis of BTP is routinely used in clinical practice and is highly supported by oncology and pain experts. The algorithm is based on three simple questions (Figure 1).

1. Does the patient have background pain?
2. Is the background pain adequately controlled?
3. Does the patient have transient exacerbations of pain?
Rapid onset opioids for the management of BTcP

The APM task group guidelines recommended oral opioids as the “rescue medication” of choice in the management of breakthrough pain episodes. However, given the onset of action time of morphine (approximately 30 minutes) and time to peak effect (approximately 60 minutes) this would mean that half of the patients who take morphine for BTcP, get no relief from pain and have excess opioid in their system afterwards. This is a controversial area as rapid relief has been described for patients with BTcP after taking morphine. It is possible that the relief is due to the spontaneous resolution of the breakthrough pain or potentially a placebo effect.

Rapid onset opioids (ROOs), such as sublingual fentanyl tablets (ABSTRAL®; Product Information), have a rapid onset and short duration of action that mimic the median time of onset and duration of breakthrough pain described in the Davies et al study.

The decision to use a specific opioid preparation should be based on a combination of the pain characteristics (onset, duration), the product characteristics (pharmacokinetics, pharmacodynamics), the patient’s previous response to opioids and the patient’s preference.

Clinical features of BTcP

The clinical features of BTcP depend on the precipitating event. A survey of 1000 patients showed breakthrough pain can vary in intensity, frequency and duration, and that patients can have more than one type of breakthrough pain. This can make it a difficult condition to manage.

The time to peak intensity and duration of the breakthrough pain is critical to the management of BTcP because different medications have different onset and duration of action times. In the Davies et al. study, the median time to peak intensity was 10 minutes and ranged from 1 minute to 240 minutes (Figure 2). The median duration of the breakthrough pain was 60 minutes and ranged from 1 minute to 360 minutes (Figure 2). The median duration was longer for spontaneous pain (60 minutes) than for incident pain (45 minutes). In terms of pain severity, the majority of patients (~62%) rated their BTcP as severe and 34% rated it as moderate.

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The ideal rescue medication has the following characteristics:

- Good efficacy
- Rapid onset of action
- Short duration of effect
- Good tolerability
- Easy to use
- Acceptable to the patient
- Available / affordable
- Can be given by carer
- Low risk of addiction or diversion
How the management of breakthrough cancer pain is evolving

Table 1. Prescription-adjusted (per 100,000 prescriptions) relative risk of abusing each compound

<table>
<thead>
<tr>
<th>Compound</th>
<th>Hydrocodone</th>
<th>IR oxycodone</th>
<th>IR fentanyl</th>
<th>IR hydromorphone</th>
<th>IR morphine</th>
<th>IR oxymorphone</th>
<th>ER oxycodone</th>
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*p < .0001, †p < .001, ‡p < .01, *p < .05. ER = extended release; IR = immediate release.

Frequency and dose of rescue medication

The Product Information for all ROOs recommend a maximum frequency of 4 doses per day. This is based on the maximum dose frequency used in the pivotal clinical trials rather than on pharmacology data.

It is important that the dose of opioid rescue medication is determined by individual dose titration, as recommended in the APN guidelines and the Product Information for each medication. The optimal dose is a balance between analgesia and side effects.

Some experts and guidelines recommend proportional dosing to manage BTcP, however this can overdose patients and doesn’t necessarily achieve the best pain management possible for every patient. Ideally every patient should be started on a low dose of ROO and be titrated up. When titrating dose, it is important to discuss the process with the patient, ensure they have access to health care professional support and advise on appropriate use of additional rescue analgesics during titration.

Is abuse and addiction a concern?

Rapid onset opioids can be safely used according to the indication, yet there is a lot of discussion in the literature about misuse, abuse and addiction. Definitions of abuse, misuse and addiction vary; the following are based on elements that occur in at least two different definitions:

- Misuse – Use that contradicts medical advice or that is not prescribed; is restricted to prescription or over-the-counter medications and for a medical purpose
- Abuse – Use for nontherapeutic, recreational purposes to obtain psychotropic or euphoric effects and in a way that contradicts medical advice or is not prescribed
- Addiction – Compulsive use despite harm or negative consequences; chronic disease, impaired control, craving or neurobiological dysfunction.

Drug addiction is relatively uncommon in cancer patients, and there is occasionally misuse and abuse. Addiction is related to activation of the dopaminergic reward system, and avoidance of opioid withdrawal is an aim among drug addicts. Rapid onset may seem like a positive factor for addicts, however, their short duration is a negative factor, which means ROOs are not ideal drugs for addiction.

Data from a US study of drug addicts revealed that oxycodone was the opioid of choice in more than 50% of cases while fentanyl was the preferred opioid in less than 10% of cases. In another study involving 7,000 drug addicts, the relative risk of abuse was determined by individual dose titration, as recommended in the APN guidelines and the Product Information for each medication. The optimal dose is a balance between analgesia and side effects.

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Conclusion/Take home messages

There are two types of breakthrough pain, spontaneous and incident, and for breakthrough pain to exist there must be good control of background pain. BTcP is a heterogeneous condition that can significantly impact a patient’s quality of life and daily activities.

Management of BTcP needs to be individualised to each patient, with a goal to achieve balance between the best pain management possible and tolerable side effects.

There is no one size fits all medication for BTcP and the choice of medication depends on patient preferences and goals, pain characteristics, and the properties of the medication.

The dose of ROO rescue medication should be determined by individual dose titration, and reassessment of breakthrough pain should occur as part of the patient’s management.

There is a low risk of ROO medications leading to addiction in cancer patients.

References