

Breakthrough pain should be distinguished from background pain



Dr Giovambattista Zeppetella discusses the new guideline from the Association for Palliative Medicine on the management of breakthrough pain in patients with cancer

Pain is a common feature of cancer. It is one of the most feared consequences of the disease and presents a significant clinical challenge. As pain assessment and management strategies have evolved it has become increasingly clear that patients with cancer often report variations in their pain during the course of the day. Even when background pain is well controlled, many patients with advanced cancer may experience brief, self-limiting exacerbations of severe pain known as breakthrough pain.¹ In 2008, the Association for Palliative Medicine of Great Britain and Ireland (APM) produced new guidance on *The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland.*²

Characteristics of breakthrough pain

The reported prevalence of breakthrough pain varies from 24% to 95%, depending on the population and survey methodology.³ Among adults with cancer, it is prevalent at all stages of disease, but is most common among those with advanced disease and poor

performance status.⁴ On a practice list of 10,000 patients, there will be approximately 25 deaths from cancer per annum, and 10–15 patients will have breakthrough pain.

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Breakthrough pain is a heterogeneous problem and its occurrence is an indication of a distinct clinical predicament that requires independent assessment and targeted treatment. Patients often have multiple

breakthrough pains. A typical breakthrough pain episode has the following characteristics:^{3,5}

- ▶ a fast onset
- ▶ is often very severe
- ▶ usually reaches peak intensity within a few minutes
- ▶ an average duration of approximately 30 minutes.

Two sub-types of breakthrough pain exist:⁵

- ▶ incident pain—can be precipitated by predictable volitional factors such as movement or unpredictable non-volitional factors such as bladder spasm
- ▶ spontaneous pain—occurs in the absence of a specific trigger and can be unpredictable and occurs at random.

Breakthrough pain co-exists with adequately controlled background pain and should, therefore, be distinguished from end-of-dose pain that relates to decreasing analgesia levels at the end of the dose interval, usually because of an inadequate analgesic dose or too long an administration interval.⁵

Despite the self-limiting nature of breakthrough pain it can place significant physical, psychological, and

economic burdens on patients and their carers. Patients with breakthrough pain are often less satisfied with their analgesic therapy, they have decreased functioning because of their pain, and they may also experience social and psychosocial consequences, such as increased levels of anxiety and depression.^{5,6} Breakthrough pain can be a poor prognostic indicator, and the site of breakthrough pain may predict the response to treatment. Furthermore, if inadequately relieved, breakthrough pain can place additional financial burdens on patients and on the healthcare system.³

Need for a new guideline

Despite breakthrough pain being recognised for 20 years,¹ there is little guidance on its management. An expert working group of the European Association for Palliative Care produced a consensus document in 2002, which in part addressed the management of cancer-related breakthrough pain.⁷ In addition, Bennett et al produced an industry sponsored consensus document in 2005, which addressed the management of all types of breakthrough pain.⁸

In view of the above, it was decided to assemble an independent, multi-professional task group to produce some up-to-date, evidence-based, practical, clinical guidelines on the management of cancer-related breakthrough pain in adults.² The task group was convened in accordance with internal APM guidelines. The participants all work in palliative care in the UK. The evidence from literature was graded according to the SIGN grading system for recommendations in evidence-based guidelines.⁹

Defining breakthrough pain

The definition of breakthrough pain varies in the literature—some investigators have described breakthrough pain only after background pain has been controlled,¹ while others define it irrespective of analgesic

regimen or in patients with uncontrolled background pain who experience exacerbations.¹⁰ The lack of consensus on a formal definition has led to difficulties when comparing studies and recommending management strategies.¹⁰ In order to emphasise the distinction between uncontrolled background pain and breakthrough pain the guideline development group proposed the following definition:²

'Breakthrough pain ... 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.'

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If inadequately relieved, breakthrough pain can place additional financial burdens on patients and on the healthcare system

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The APM guideline suggests three questions that would be helpful for GPs to use during diagnosis to distinguish between uncontrolled background and breakthrough pain:²

- ▶ Does the patient have background pain?
- ▶ Is the background pain adequately controlled?
- ▶ Does the patient have transient exacerbations of pain?

If the patient answers 'yes' to all three questions, then they have breakthrough pain.²

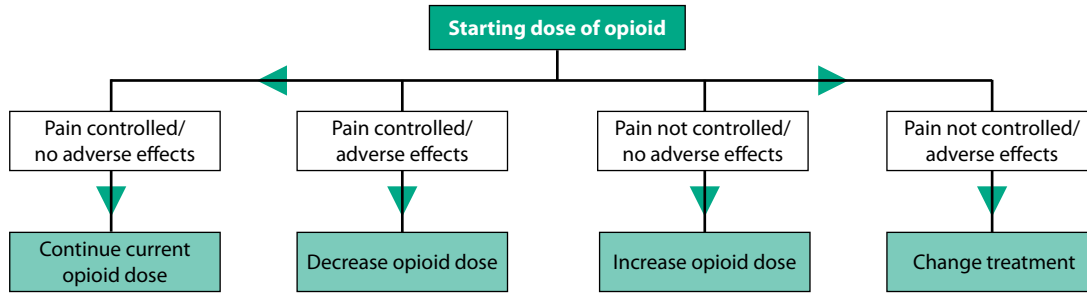
How the guideline will improve breakthrough pain management

The literature on breakthrough pain clearly identifies the need for improved management.^{2,5} A number of factors contribute to sub-optimal management including diagnosis, assessment, and re-assessment of breakthrough pain. The APM guideline aims to address these by clearly defining breakthrough pain (see above) and, in particular, distinguishing it from background pain.

Recommendations from the guideline can be applied in all settings including primary care as patients are cared for at home for the majority of their illness. There is also a suggested schedule for assessment and reassessment, which includes: assessing the onset, frequency, site, radiation, quality, intensity, and duration of pain, exacerbating or relieving factors, the response to analgesics and other interventions, associated symptoms, and determining interference with activities of daily living. The guideline also addresses the challenge of primary care management.²

Breakthrough pain is commonly treated with supplemental doses of oral opioids—so called 'rescue medication'. The commonest method of providing rescue medication is with normal-release formulations of morphine. Although the most effective dose of rescue medication remains unknown, a fixed proportion of the around-the-clock dose is usually advised.¹¹ An oral opioid may take 30–40 minutes to provide relief,¹² whereas the peak pain intensity of breakthrough pain can occur in as little as 3 minutes.¹³ This could result in partially effective breakthrough pain management and troublesome adverse effects such as nausea and drowsiness. Other oral opioids (e.g. oxycodone, hydromorphone) may have similar limitations.¹²

Figure 1: Recommended dose titration schedule for opioid rescue medication²



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A number of factors should be taken into account when selecting the appropriate drug:⁷

- ▶ class of drug
- ▶ route of administration
- ▶ dosage
- ▶ patient setting
- ▶ breakthrough pain subtype.

The ideal rescue medication should be efficacious and patient friendly, with a rapid onset of action, a relatively short duration of action, and minimal adverse effects.¹² Although the oral route is often preferred for rescue medication, the typical clinical and dynamic characteristics of breakthrough pain suggest that responsiveness to an oral drug may be less than optimal. Non-parenteral drugs with faster onset of effect on breakthrough pain have now been developed—the transmucosal fentanyl formulations.

Traditionally, the dose of opioid rescue medication has been a fixed proportion of the dose of the opioid background medication. Data from controlled trials with oral transmucosal fentanyl formulations suggest that there is no relationship between the most effective dose of these preparations and the effective dose of the background opioid. Thus, on the basis of this (and anecdotal data with conventional products), the guideline recommends that the dose of all opioid rescue medication should be determined

by individual titration (see Figure 1, p.XX).²

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Summary of the APM recommendations

On the basis of a literature review, the APM task group was unable to make recommendations about any individual interventions, but was able to make a series of 12 recommendations about certain generic strategies (Box 1, p.XX). Unfortunately, most of the recommendations are based on limited evidence (grade of recommendation= D),²

i.e. from non-analytical studies or so-called ‘expert opinion’.

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Promoting best practice in primary care

The successful management of cancer pain depends on a comprehensive pain assessment, which must take into account both background and breakthrough pain. As breakthrough pain is a heterogeneous phenomenon that can vary from individual to individual, and within an individual over time, a comprehensive assessment of its frequency, intensity, rate of onset, duration, and predictability is required.²

The aim of breakthrough pain management is to reduce the intensity, severity, and impact of each bout of pain. A holistic framework is recommended that includes:

- ▶ general assessment (pain assessment, explanation)
- ▶ lifestyle changes (coping strategies)
- ▶ management of reversible causes (incident pain precipitants)
- ▶ modification of the pathological processes (anti-neoplastic therapies)
- ▶ symptomatic management of breakthrough pain (pharmacological and non-pharmacological, see Figure 2, p.XX)
- ▶ reassessment (evaluation of pain and management)

Box 1: Summary of the Association for Palliative Medicine of Great Britain and Ireland recommendations for the management of cancer-related breakthrough pain²

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

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The following series of questions may help in the assessment, diagnosis, and management of breakthrough pain:²

- ▶ Onset of pain?
- ▶ Frequency of pain?
- ▶ Site of pain?
- ▶ Radiation of pain
- ▶ Quality (character) of pain?
- ▶ Intensity (severity) of pain?
- ▶ Duration of pain?
- ▶ Exacerbating factors?
- ▶ Relieving factors?
- ▶ Response to analgesics?
- ▶ Response to other interventions?
- ▶ Associated symptoms?

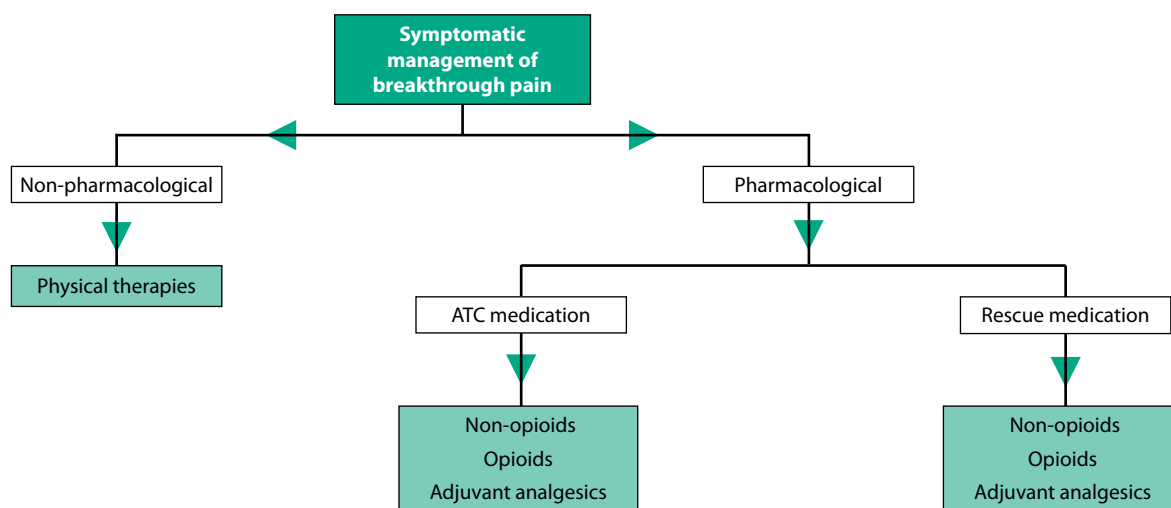
If the pain fails to respond to first-line treatment referral to a specialist may be considered.

Key priorities for implementation

In order to reduce the impact of breakthrough pain in patients with cancer:

- ▶ healthcare professionals need a clearer understanding of breakthrough pain and the impact that it has on both patients and their carers
- ▶ all healthcare professionals should include an assessment of breakthrough pain in their overall pain assessment

Figure 2: The symptomatic management of breakthrough pain



ATC=around-the-clock

- ▶ patients need more education and information to increase their understanding of breakthrough pain and to manage their expectations
- ▶ close working relationships between primary care and oncology and palliative care specialists for managing those pains resistant to common analgesic therapies.

With two new products available for the management of breakthrough pain in the form of fentanyl citrate, and others soon to be marketed, better understanding of this clinical problem will ensure that these products are used appropriately and cost-effectively.

A website dedicated to providing expert opinion and information about breakthrough pain, and where content is vetted and endorsed by an independent international editorial panel of pain experts, may be a helpful resource for healthcare professionals: see www.breakthroughpain.eu.

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Practice-based commissioning take home messages

written by Dr David Jenner, NHS Alliance PBC Lead

- ▶ Breakthrough pain is common and can be difficult to adequately treat with traditional analgesic preparations
- ▶ The careful and thorough assessment of background and breakthrough pain is key for patients with cancer
- ▶ Commissioners should consider specific requirements for pain assessment and control when specifying 'end-of-life' care pathways
- ▶ Close coordination between specialist and palliative care services and medical and nursing staff in primary care will be essential to respond to individual needs.
- ▶ New trans-mucosal fentanyl preparations may have a role to play but are expensive ~£6.19 a dose (various strengths)^a

^aBritish National Formulary. *BNF 56*. London: Royal Pharmaceutical Society, 2008.

d'Oncologia, Spain; and Dr Bee Wee, University of Oxford, UK.

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