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PRACTICE GUIDELINE

# Canadian recommendations for the management of breakthrough cancer pain

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## ABSTRACT

Breakthrough cancer pain (BTCP) represents an important element in the spectrum of cancer pain management. Because most BTCP episodes peak in intensity within a few minutes, speed of medication onset is crucial for proper control. In Canada, several current provincial guidelines for the management of cancer pain include a brief discussion about the treatment of BTCP; however, there are no uniform national recommendations for the management of BTCP. That lack, accompanied by unequal access to pain medication across the country, contributes to both regional and provincial variability in the management of BTCP.

Currently, immediate-release oral opioids are the treatment of choice for BTCP. This approach might not always offer optimal speed for onset of action and duration to match the rapid nature of an episode of BTCP. Novel transmucosal fentanyl formulations might be more appropriate for some types of BTCP, but limited access to such drugs hinders their use. In addition, the recognition of BTCP and its proper assessment, which are crucial steps toward appropriate treatment selection, remain challenging for many health care professionals.

To facilitate appropriate management of BTCP, a group of prominent Canadian specialists in palliative care, oncology, and anesthesiology convened to develop a set of recommendations and suggestions to assist Canadian health care providers in the treatment of BTCP and the alleviation of the suffering and discomfort experienced by adult cancer patients.

**Key Words** Breakthrough cancer pain

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## INTRODUCTION

Despite recent advances in diagnosis, assessment, and treatment, breakthrough cancer pain (BTCP) continues to present a significant challenge for patients, their caregivers, and health care professionals. Furthermore, because of a lack of uniform Canadian guidelines and recommendations about the management of BTCP, significant provincial, regional, and inter-institutional variations in therapeutic approaches persist. To streamline the management of BTCP across the country, a group of prominent Canadian clinicians involved in the care of cancer pain, including individuals with expertise in anesthesiology, oncology, and palliative care, were gathered by the two co-chairs of the expert panel. The members of the expert panel are involved clinically and academically, particularly in the teaching of pain management. Each of the clinicians has participated in research, and all have published in their respective fields. Based on relevant literature, recent evidence, anecdotal reports, and personal experience, the experts developed a set of recommendations and suggestions, with the objective of guiding Canadian clinicians in the treatment of BTCP in daily practice. The main goal was to assist Canadian health care providers and policymakers in the decision-making process and thereby to improve outcomes and quality of life for patients with cancer.

## METHODS

A search of the English-language literature in PubMed and the Cochrane Library used the terms "breakthrough cancer pain" or "cancer pain" to identify relevant studies published from January 2008 to December 2014. However, the literature search was not limited to that period, because it was followed by a manual search of references cited in selected papers published in peer-reviewed journals. Meta-analyses, systematic reviews, and randomized clinical trials were the preferred sources.

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The search was refined according to specific topics determined during a consultation process with the expert panel members. Subsequently, each member of the expert panel was assigned a specific topic for which that member reviewed selected references to ensure relevance and acceptable methodologic quality. The key findings were presented and discussed during a consensus meeting that took place 24 January 2015 in Montreal, Quebec. During the meeting, the experts reviewed the evidence and formulated recommendations, taking into consideration the benefits, risks, and side effects of various interventions. Consensus was reached by discussion during the meeting. The resulting manuscript was further revised by the entire group. Revision comments were discussed by the group, agreed upon, and integrated.

The guidelines highlight key points from the data in three ways:

- "Consensus points" are evidence-based statements concerning the current understanding of BTcP diagnosis and management.
- "Education points" are identified unmet needs and challenges for which additional learning activities might be required.
- The 8 general recommendations that were formulated can be used to guide clinical practice and management of BTcP in Canada.

The recommendations presented here are not a replacement for clinical judgment and cannot be used as a legal resource because they do not provide individual guidance in all situations. In fact, when considering therapeutic approaches for cancer pain, health care providers must consider the needs, preferences, values, financial situation, and personal context for each individual patient.

## BTcP: COMMON CHARACTERISTICS AND CONTRIBUTING FACTORS

Pain is a common occurrence in patients with cancer and especially in those with advanced disease[1]. Cancer pain is multifactorial in nature and can be classified according to its pathophysiology (nociceptive, neuropathic), cause (related or unrelated to the disease and its treatment), and the timing of its occurrence[1,2]. Breakthrough pain represents a key element of pain management in patients with malignancies.

The first standardized definition of BTcP was established by Portenoy *et al.*[3] in 1990 and amended by Davies *et al.*[4] in 2009. According to those two groups, BTcP is a temporary exacerbation of pain that occurs despite adequately controlled background pain. Pain episodes occurring without background pain or with poorly controlled background pain cannot therefore be classified as BTcP. Figure 1 sets out the algorithm for the identification of BTcP proposed by Davies *et al.*[4] in 2009.

The classical description of BTcP includes rapid onset, short duration, moderate-to-severe intensity, and frequent occurrence. Although BTcP can last up to 60 minutes, the typical duration of an episode is 15–30 minutes[3–6]. Another important distinguishing characteristic of BTcP is its rapid onset, with escalation to maximum intensity in as little as 1 minute[3–7]. The frequency of the pain episodes can vary from a single time to several times daily or weekly[7,8]. However, frequent occurrence of BTcP can be indicative of uncontrolled baseline pain and a need to revisit the therapeutic approach for background pain.

Although some authors also consider end-of-dose pain as a subtype of BTcP, this type of pain, caused by declining analgesic levels, is a consequence of poorly controlled background pain and does not represent true BTcP[4]. Rather, it indicates that the around-the-clock analgesic approach should be re-assessed.

Breakthrough cancer pain can be divided into two categories: incident (predictable) and spontaneous (idiopathic, unpredictable) pain (Figure 2). Incident BTcP is related to a specific identifiable cause and can be subclassified into one of three categories[9]:

- Volitional incident pain (initiated by a voluntary act such as walking)
- Non-volitional incident pain (initiated by an involuntary act such as coughing)
- Procedural pain (initiated by a therapeutic intervention such as wound dressing)

Approximately 50% of BTcP episodes are precipitated by a voluntary or involuntary event[10].

The manifestation of BTcP is influenced by numerous patient-, cancer-, and treatment-related factors and changes throughout the course of the disease[1]. Factors directly related to cancer include compression or infiltration of hollow organs, soft tissue, bones, and nerves. Causes indirectly related to cancer include the consequences of disease (coughing because of lung cancer, herpes zoster or post-herpetic neuralgia because of a compromised immune system, back pain because of

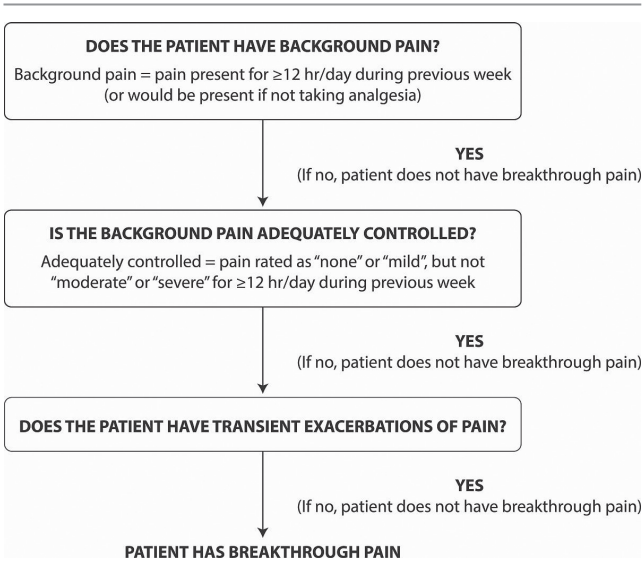


**FIGURE 1** Algorithm for the assessment of breakthrough cancer pain. Reproduced with permission from Davies *et al.,* 2009[4].

immobility) or its treatment (investigational procedure, chemotherapy, radiation, surgery), or both. Pre-existing conditions or those that arise independently of cancer (arthritis, migraine) are recognized as a source of pain in 3%–10% of cancer patients[1]. Patient and physician attitudes toward the disease and its treatment can also contribute to breakthrough pain. Breakthrough cancer pain is frequently misunderstood by health care professionals, leading to poor assessment and undertreatment. Furthermore, given that cancer pain has physical, psychological, social, and spiritual dimensions, determination of the contribution of the various factors can be difficult. Clinicians should also be aware of chemical coping, because the reported incidence of pain in some patients might reflect their psychological distress rather than their physical pain[11].

## Consensus Points

- Differentiation between BTcP and background pain is challenging. Many clinicians perceive cancer pain as one entity and often consider BTcP to be part of baseline pain. That belief likely contributes to a high incidence of BTcP, its under-recognition, and undertreatment. Adequate control of background pain is the key characteristic that should be taken into consideration when assessing BTcP.
- End-of-dose pain is understood to be the reappearance of background pain because of an insufficient dose of around-the-clock opioids either in short- or long-acting forms. The end-of-dose effect is often a result of a lack of knowledge about pharmacokinetic parameters. It and BTcP have different causes and should be assessed and treated differently.
- Although mild pain (intensity 2–3 on a 10-point scale) might not require immediate attention, it might be a sign of progressive disease and, as such, it requires proper follow-up.

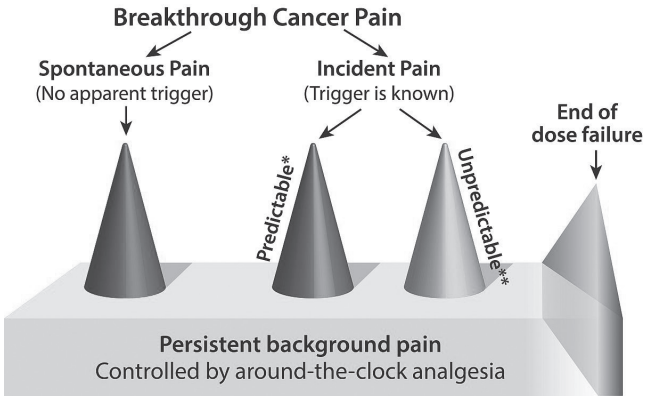


**FIGURE 2** Classification of cancer pain according to its occurrence. * Predictable pain can be further divided into pain induced by a specific procedure or treatment (for example, changing a wound dressing) and pain induced by voluntarily movement (for example, walking). ** Pain precipitated by an involuntary act (coughing, bladder spasm, movement during sleep).

## Education Points

- Health care professionals have to understand the pathophysiology of pain to be able to perceive that transient sharp spikes of pain, as illustrated in Figure 2, are separate entities with causes and manifestations that are different from those of background pain. In addition, BTcP is multifactorial in nature; it should be treated according to its suspected pathophysiology to optimally reduce its incidence, prevalence, and severity.
- Clinicians have to understand that not all incident pain experienced by cancer patients can be categorized as breakthrough pain. For example, movement-related pain experienced by a patient with bone fractures who does not require around-the-clock analgesia should not be considered breakthrough pain. On the other hand, incident pain, as described in this case, if present most of the day, should be treated as background persistent pain.
- Differentiation of end-of-dose pain from BTcP could require that health care professionals, caregivers, or patients keep a log and document frequency, timing, duration, severity, and trigger (if known) of pain episodes. Such documentation requires time and training, and in many instances might be compromised by factors such as a patient's cognitive functioning, busy schedules and a lack of knowledge on the part of residential care staff, or inadequate orders from treating clinicians, underlining a clear need for education initiatives.

# EPIDEMIOLOGY AND CONSEQUENCES OF BTcP

The reported prevalence of BTcP varies significantly across studies and regions[12], principally because of variability in the definitions of BTcP, study designs, methods used to assess BTcP, settings, and patient populations. According to a recent systematic review of the published literature that included nineteen studies and more than 6000 patients with cancer pain, the prevalence of BTcP ranges from 33% to 95%, with an overall pooled prevalence of 59.2%[12]. That finding is similar to the reported prevalence of breakthrough pain in patients with chronic non-cancer pain[13–15].

The prevalence of BTcP is lowest in studies conducted in outpatient clinics (39.9%) and highest in studies conducted in the hospice setting (80.5%)[12]. The higher reported prevalence of BTcP in the hospice setting has several possible explanations beyond the fact that the patients might have more advanced disease. Compared with other specialists, most clinicians in hospices have more knowledge and experience in recognizing BTcP. Also, the era in which a study was performed could be an important factor; the BTcP prevalence rate has decreased to 49% in the most recent publications from 75% in studies published during 1990–1994[12]. The difference potentially reflects a better understanding of the pathophysiologic mechanisms and clinical features of BTcP, the overall changes in its definition and diagnosis, and more effective therapeutic approaches. For example, improvements in diagnostic criteria might have excluded several situations (end-of-dose failure, for

instance) that were previously considered to be BTCP. Better control of background pain and use of co-analgesia could also be a contributing factor.

According to a study conducted in 110 centres in Italy, patients with BTCP ($n$ = 1801) are younger and have more bone metastases and neuropathic pain[16]. That observation might be a reflection of clinician reluctance to prescribe opioids to younger patients and of the fact that younger patients tend to be more active. However, given that incident pain was not distinguished from other types of pain, it is difficult to further validate the latter assumption.

In a questionnaire completed by 1000 patients (treated at 28 palliative care units in 13 European countries) about the characteristics of their BTCP[10], 44% of respondents reported incident pain, 42% reported spontaneous pain, and 14% indicated that they experienced a combination of incident and spontaneous breakthrough pain. Patients with incident pain reported that the pain interfered mostly with their ability to walk and perform daily activities; those with spontaneous pain said that their pain interfered mostly with their mood and ability to sleep.

A recent survey of cancer patients ($n$ = 94) conducted at four Canadian cancer centres revealed that, in approximately one half the patients, an episode of cancer pain lasts about 60 minutes[17]. The average pain score was 7.8 on a 10-point scale, indicating severe pain, and 96% of participants indicated that pain affected their activities of daily living (>50% were unable to work or sleep). In a similar study conducted in Europe, 32% of patients revealed that their pain was so severe they "want[ed] to die"[18]. Patients with BTCP also report loss of control, changes in lifestyle, and diminished quality of life[19]. In addition, for many patients, pain is a reminder of the presence of cancer, and they often associate the severity of pain with the severity of their disease (that is, mild or no pain equals remission, and severe pain equals progressive disease).

With regard to economic impact, BTCP is associated with an increased number of hospitalizations, longer hospital stays, and more emergency room and physician office visits, totalling to US$12,000 annually in costs for patients with BTCP compared with US$2400 annually for those without BTCP[20]. From the patient and caregiver perspectives, BTCP incurs significant personal expense, including factors such as transportation to clinic or hospital, parking, change in medications, nonpharmacologic therapies, and childcare[21]. For providers and institutions, treatment of poorly managed BTCP substantially raises the costs of care and places additional demands on health care resources[21].

### Consensus Point

- Approximately 60% of cancer patients in Canada experience breakthrough pain, which significantly affects quality of life, daily activities, and psychological well-being, because the intensity of pain is often associated with the severity of the disease. This BTCP also poses a significant burden on caregivers and the health care system.

### Education Points

- Education initiatives for patients are necessary, because patients with a better understanding of the causes of their pain will be better able to manage their pain and properly use prescribed medications.
- Clinicians should be aware of the significant burden that BTCP is causing to patients and their families and should work closely with other members of their health care team to alleviate that burden, reduce the fears and anxieties of patients, and make patients as comfortable as possible.
- Additional education efforts are required to assist clinicians in recognizing the underlying mechanisms and pathophysiology of idiopathic BTCP, because this type of pain can have detrimental effects on the mood and well-being of patients. Patients with spontaneous unpredictable pain often live in fear and worry because a sharp spike of pain can happen at any time, without apparent cause. Thus, clinicians should strive to identify and, if possible, treat the pathophysiology behind idiopathic pain so as to alleviate that psychological burden from patients and their caregivers.

## ASSESSMENT GUIDES AND TOOLS

The main objectives of clinical assessment of BTCP are to

- find a correctable cause, if possible;
- differentiate baseline persistent pain from BTCP; and
- determine the pattern of pain.

Table I lists potential questions for the assessment of BTCP. It has been reported that many palliative care nurses feel challenged in differentiating BTCP from poorly controlled background pain[22]. A recent survey of 104 nurses at 10 British palliative care services revealed that 82% of nurses wanted more training in the assessment of BTCP[23]. Another survey of 1241 European nurses showed that although 39% had no pain assessment tool to help distinguish between types of pain, 95% of those who used a tool found it useful[24]. Similarly, in Canada, as many as two thirds of nurses use assessment tools and guidelines to help distinguish between background pain and BTCP[25], finding those tools or guidelines to be somewhat (55%) or very (42%) useful.

**TABLE I** Questions that can help in the assessment of breakthrough cancer pain

| |
|---|
| Do you have episodes of severe pain? |
| How many episodes do you usually have per week or per day? |
| How long does each episode last? |
| What triggers an episode, if anything? |
| Can you describe how much an episode hurts on a scale of 0–10, if 0 is no pain at all and 10 is the worst pain imaginable? |
| Where is the pain? |
| What does the pain feel like? Is it similar to or different from your usual baseline pain? |

The current literature contains no information about the use of various tools by clinicians, likely reflecting the fact that, because of their busy schedules, they assign the pain assessment task to staff. That observation further highlights the need for education initiatives that guide nurses in the utilization of tools and clinicians in the interpretation of the information gathered. A diagnosis of BTCP is usually made based on multiple sources, but in patients with normal cognitive functioning, self-report is the best source of information about BTCP[26].

Overall, the tools for pain assessment can be divided into unidimensional tools, multidimensional tools, and pain diaries. Pain diaries provide a detailed patient-reported account of the pain's nature, duration, severity, and predictability. If properly completed, the diary can be useful in evaluating the frequency and intensity of BTCP over time[27]; however, patient compliance with diary completion is typically poor.

The 3 unidimensional pain scales (Figure 3) for pain intensity measurement—visual analog scale (VAS), numeric rating scale (NRS), and verbal rating scale (VRS)—have all been proved to be reliable and valid[28]. The preference of patients for a particular tool varies. For example, a VRS tends to be preferred by older individuals and by those with lower levels of education. However, in a systematic review of 54 studies comparing unidimensional scales, a NRS demonstrated better compliance in 15 of 19 studies comparing it with a VAS and a VRS, and it was the recommended tool in 11 studies on the basis of higher compliance rates, better responsiveness and ease of use, and good applicability relative to a VAS or VRS[28]. Brunelli *et al.*[29] also demonstrated that, in cancer patients, a NRS was better than a VAS in distinguishing between background pain and peak pain intensity, with a lower proportion of patients giving inconsistent evaluations (14% vs. 25%). In addition a NRS showed higher reproducibility in the measurement of pain exacerbation. To that end, the European Palliative Care Research Collaborative and the European Association for Palliative Care Research Network recommend using a 0–10 NRS with standard endpoints of "no pain" and "pain as bad as you can imagine"[30] to measure cancer pain intensity.

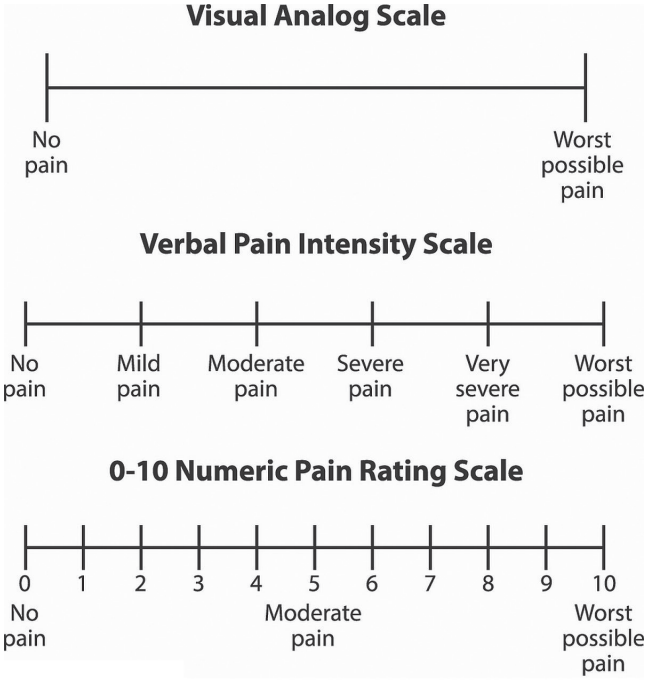


**FIGURE 3** Unidimensional pain scales.

Multidimensional tools such as the Brief Pain Inventory[31] and the McGill Pain Questionnaire[32] provide specific information about factors such as the effect of pain on daily function, the location of pain, and the effectiveness of treatments. Those tools tend to be complex and to present challenges for patients with cognitive impairment. In addition, none of the tools for general pain assessment differentiate between BTCP and background pain.

Two recently developed BTCP-specific tools are the Alberta Breakthrough Pain Assessment Tool (ABPAT)[33] and the Breakthrough Pain Assessment Tool (BAT)[34].

The ABPAT was developed using a Delphi process involving a literature review by an international group of experts, followed by a pre-test with think-aloud interviews of patients with BTCP[33]. The patient self-reporting section of the tool (15 questions) assesses the relationship of pain flares to background pain, further probes for details about sources of relief, and inquires about timing, frequency, location, severity, quality, causes, and predictability of the BTCP. The tool was validated in 249 patients from 7 different centres[35]. Nearly all the participating patients (92.8%) stated that the questions were easily understandable, and 87.1% said that the tool explained the BTCP problem. Physician–patient correlation tests showed statistical significance. The tool was also able to assess the satisfaction of patients with their BTCP medication. Use of the ABPAT to evaluate the efficacy of breakthrough medication revealed that 78.2% of patients claimed to have good pain relief, but only 55.9% of patients were satisfied with the time of onset of action for the medication.

The development of the BAT followed a procedure similar to that of the ABPAT (literature review, Delphi process, and semistructured interviews with patients experiencing BTCP)[34]. The tool was also subjected to a series of psychometric tests for factor structure, validity (content and construct), reliability (internal consistency, test–retest), and responsiveness to change. Where the ABPAT tool was designed specifically for research purposes, the objective of the BAT was to facilitate the management of patients with BTCP in the clinical setting.

## Consensus Points

- Breakthrough pain can be difficult to assess in the clinical setting. We recommend the algorithm proposed by Davies *et al.*[4] (Figure 1) because it is widely used and cited in the literature.
- An assessment tool can be an effective way to evaluate and document the characteristics of BTCP. However, the tool has to be quick and simple to use. We recommend the 0-10 NRS because it is currently accepted as the standard.

- Because a thorough assessment is a key step toward adequately managing BTCP, clinicians should strive to identify the origin of the pain (cancer, treatment, comorbidities, or some combination thereof), the pathophysiology (nociceptive, neuropathic, or mixed), and any other factor that could affect treatment.
- We recognize that recently developed BTCP assessment tools have the potential to be used for clinical and teaching purposes. However, follow-up studies of the outcomes in patients who are assessed and subsequently managed using those tools are needed.

### Education Points

- Education initiatives to guide health care personnel in the use of BTCP assessment tools are needed. Furthermore, although the ABPAT was developed for research purposes, and the BAT, for clinical purposes, those tools could be used to aid in the decision-making process in complicated cases. Thus, palliative care nurses and clinicians have to be trained in how to use those tools and the situations in which the tools can be helpful. The availability of BTCP assessment tools and the education initiatives relating to their use will also build awareness that BTCP is a unique entity and not just a part of background cancer pain.

## CONVENTIONAL MANAGEMENT OF BTcP

According to World Health Organization guidelines, opioids are the mainstay of analgesic therapy in cancer patients and are classified according to their ability to control pain[36]. Morphine is traditionally considered the first opioid choice for the treatment of moderate-to-severe cancer pain, and it is the most studied opioid[37,38]. However, since the mid-1990s, the use of other opioids such as oxycodone, fentanyl, hydromorphone, and methadone have significantly increased. Immediate-release oral opioids are currently the approach most commonly used to manage BTCP.

Conventional treatment of BTCP often involves taking, as "rescue" medication, an extra dose (at 5%–20% of the total daily dose) of the opioid used around the clock to relieve background pain[39,40]. That approach, which is based entirely on many years of clinical experience, might not always offer the optimal speed of onset and the duration needed to match the rapid-onset nature of an episode of BTCP. Because the pain relief could be urgently required, routes of administration designed to deliver drugs rapidly (that is, parenteral or transmucosal) are then chosen. A few studies have looked at the sublingual use of morphine; however, because of its hydrophilic properties, morphine is not the best candidate for that route of administration[41]. It has been suggested that sublingual methadone—because of its good bioavailability and highly lipophilic nature, allowing it to be readily absorbed via the sublingual mucosa—might be an interesting option for breakthrough pain[42–44].

The use of the same opioid treatment for baseline persistent pain and BTCP could offer some advantages, such as easier titration of the around-the-clock dose and better management of opioid side effects; however, that approach might not always be feasible, because the pharmacokinetics of around-the-clock opioids might not match the onset of the BTCP episode. As mentioned, oral administration of morphine, although effective in the management of chronic pain, might not be suitable for the treatment of BTCP because of its particular pharmacokinetic profile (hydrophilic nature, start of analgesic activity only 30 minutes after administration, and relief duration of at least 4 hours). Oxycodone and hydromorphone have similar properties. It is also speculated that the use of opioids with different pharmacologic properties and modes of action than the agent used for around-the-clock analgesia might be beneficial, because alternative pain pathways might be targeted. However, a lack of clinical trials comparing various BTCP management strategies contributes to ongoing dilemmas about the approach to use in particular situations. Thus, it is important to emphasize that the choice of opioids for basal pain and for BTCP should be based on clinical judgment and be personalized according to the patient's clinical needs, characteristics, compliance, and preference.

Some episodes of BTCP can be treated with non-opioids, such as nonsteroidal anti-inflammatory drugs, steroids, bisphosphonates, or tramadol[38,45–47]. Tramadol is a centrally acting analgesic with weak mu-receptor affinity that also inhibits the reuptake of norepinephrine and serotonin[45]. Steroids can help with pain from nerve and spinal cord compression, liver pain, and bone pain, and are particularly effective at reducing pain caused by swelling and inflammation[46]. Because bisphosphonates lower high levels of calcium in the blood, they can help with bone pain in patients with bone metastases from various types of cancers (breast, prostate, melanoma)[47] or with cancers that begin in the bone, such as multiple myeloma[48].

Although nonpharmacologic approaches to management of BTCP have not been evaluated in clinical trials, they are often used by patients and recommended by treating clinicians. Possibilities include physiatry techniques[49,50] (application of ice or heat, orthotic devices, massage and physical therapy, transcutaneous electrical nerve stimulation, percutaneous electrical nerve stimulation) and surgical interventions.

Anesthetic approaches such as chemical neurolysis and infusion of local anesthetics, opioids, and clonidine by epidural catheter are useful in the treatment of persistent pain, but can also be beneficial in alleviating BTCP[51–53]. A percutaneous cordotomy can be used to treat refractory incident pain from bone metastases. Intrathecal phenol block and pituitary ablation have also been used to treat refractory breakthrough pain. However, the results of those invasive procedures are often suboptimal when the risks of adverse effects are considered[54].

### Consensus Points

- The first step in the management of cancer pain should be an attempt to prevent the occurrence of pain by taking into consideration its causes. Thus, appropriate therapeutic approaches that do not necessarily include opioids (for example, radiation and bisphosphonates for bone pain) should be considered. The dose of background analgesia and the management of background pain should be optimized before attempting to treat BTCP.

- It is reasonable to use up to 20% of the total daily opioid dose to treat BTcP, because, historically, that approach has been shown to be effective in a high proportion of patients. Clinicians can consider using different formulations for background and breakthrough pain. Although no clinical trials have currently demonstrated that the "two-formulations" approach is more effective, the suggested scientific rationale is that, because of different mechanisms of action and targeting of different pathways, such an approach could result in improved pain control.

### Education Point

- Conventional treatment of BTcP has involved the use of an extra "rescue" dose (at 5%–20% of the total daily dose) of the opioid used to manage background pain, or of an equianalgesic dose of another agent (transdermal fentanyl and oral morphine, for example). Because many clinicians find it challenging to calculate the appropriate opioid dose for the management of breakthrough episodes based on the around-the-clock total opioid dose, additional education initiatives might be required.

## CONTEMPORARY APPROACHES TO THE MANAGEMENT OF BTcP WITH RAPID-ONSET OPIOIDS

As already mentioned, transmucosal administration has the potential to deliver drugs more rapidly than oral administration can. The oral mucosa are easily accessible, more permeable than skin, and more richly supplied with blood, presenting an attractive route for drug delivery and allowing for lipophilic opioids to bypass first-pass metabolism. Fentanyl, a completely synthetic mu receptor–stimulating opioid, is one of the most lipophilic opioid analgesics, with a potency 100 times that of morphine[55]. Its lipophilicity enables rapid diffusion across the blood–brain barrier, and therefore diffusion into central nervous system structures. Fentanyl also quickly crosses cellular barriers, providing broad tissue distribution and rapid onset of action.

The potency, lipophilicity, and clinical efficacy of fentanyl have made it the object of intense interest for a variety of transmucosal applications[55]. Because both its onset of action and its peak plasma concentration depend on the dose and method of delivery, achievement of analgesia occurs within 1–2 minutes after intravenous administration, 10–15 minutes after buccal transmucosal delivery, and 14 hours after transdermal application. Its duration of action is usually 2–4 hours after intravenous or transmucosal administration. The drug's half-life is longer with transdermal administration because of drug deposition in the lipids of the skin, through which it is slowly released over time.

As with many opioids, fentanyl is metabolized mainly via the cytochrome P450 pathway, and drug interactions are a possibility when fentanyl is given concurrently with other drugs affecting cytochrome P3A4[56]. Thus, caution is required, because co-administration could result in an increase in fentanyl plasma concentration sufficient to cause potentially fatal respiratory depression.

Oral transmucosal fentanyl citrate was one of the first transmucosal drug formulations, developed as a fentanyl-impregnated lozenge on a stick[55]. One quarter of the fentanyl in this formulation is absorbed rapidly through the buccal mucosa, and another 25% of the total dose is absorbed through the gastrointestinal tract after it has been swallowed[57]. Clinical experience with the formulation provided some valuable insights, including the observations that there is no meaningful relationship between the successful dose of oral transmucosal fentanyl citrate and the background opioid, and that separate titration is necessary[58–60]. In addition, clinicians learned that transmucosal fentanyl should never be administered to opioid-naïve patients. The current recommendation is that patients should already be receiving an equivalent daily dose of morphine of at least 60 mg[61,62]. Titration strategy should follow the manufacturer's recommendations, and the maximum daily use should not exceed 4 doses.

Fentanyl buccal tablets are formulated for enhanced mucosal permeation by the manipulation of pH, leading to approximately 50% transmucosal absorption[61,63]. The dissolution process takes 14–25 minutes and the time to maximum plasma concentration is 35–45 minutes[61,63]. Pain relief has been observed to begin as early as 10 minutes after administration and to last throughout the 120-minute observation period[64]. In two randomized controlled trials that compared fentanyl buccal tablets with placebo, BTcP relief attained significantly favoured fentanyl buccal tablets[64,65].

Fentanyl sublingual tablets contain water-soluble particles that are coated with fentanyl and a muco-adhesive agent to help keep the tablet under the tongue, reducing the risk of swallowing[62]. Overall bioavailability is 54%. In a randomized placebo-controlled study of fentanyl sublingual tablets in 131 adult patients with BTcP, use of the tablets resulted in significant improvements in pain intensity and relief compared with placebo[66]. In phase III studies evaluating the long-term effectiveness of transmucosal immediate-release fentanyl, patients reported high levels of satisfaction with the formulation[65,67].

Intranasal fentanyl spray was developed as an alternative method of delivering fentanyl in patients with xerostomia or salivary gland dysfunction. It has a bioavailability of approximately 89%[68]. Its onset of action occurs within approximately 7 minutes, and its duration of analgesic effect is approximately 1 hour[66]. The efficacy of intranasal fentanyl spray 50–200 μg per spray was demonstrated in a phase III randomized trial that included 120 opioid-tolerant patients with BTcP[69].

Transmucosal fentanyl formulations are generally well-tolerated, with the adverse events typical of opioids, including nausea, constipation, somnolence, and headache[64,65,67,69].

Although placebo-controlled randomized clinical trials have demonstrated the efficacy of all the available transmucosal fentanyl formulations for BTcP, the lack of head-to-head comparisons makes it challenging for physicians to select an appropriate approach based on efficacy alone. Table II provides key pharmacokinetic parameters for various fentanyl formulations used for breakthrough pain. Meta-analyses have been attempted, but a firm conclusion cannot be made because of differences between the

**TABLE II** Key pharmacokinetic parameters of various fentanyl formulations for breakthrough pain[6,8,a]

| Agent[b] and available strengths | Absolute bioavailability | Fraction absorbed transmucosally | $T_{max}$ | $C_{max}$ | $AUC_{0-\infty}$[c] | $t_{\cdot}$ |
|---|---|---|---|---|---|---|
| Oral transmucosal fentanyl citrate (Actiq[d])<br>200 µg, 400 µg,<br>600 µg, 800 µg,<br>1200 µg, 1600 µg | 50% compared with intravenous fentanyl | 25% though buccal mucosa | 20–40 Minutes (range: 20–480 minutes) for doses from 200 µg to 1600 µg | 0.39–2.51 ng/mL for doses from 200 µg to 1600 µg | 102 ng·min/mL for 200 µg to 1026 ng·min/mL for 1600 µg ($AUC_{0-1440}$) | 193–386 Minutes for doses from 200 µg to 1600 µg (mean) |
| Fentanyl buccal tablets (Fentora[d])<br>100 µg, 200 µg,<br>300 µg, 400 µg,<br>600 µg, 800 µg | 65% | 48% though buccal mucosa | 35–45 Minutes (range: 20–181 minutes) for doses from 100 µg to 800 µg | 0.25–1.59 ng/mL for doses from 100 µg to 800 µg | 0.98–9.05 ng·h/mL for doses from 100 µg to 800 µg | 2.63–11.70 Hours for doses from 100 µg to 800 µg |
| Fentanyl buccal soluble film (Onsolis[e])<br>200 µg, 400 µg,<br>600 µg, 800 µg,<br>1200 µg | 71% | 51% though buccal mucosa | 60 Minutes (range: 45–240 minutes) for 800 µg dose | 0.38–2.19 ng/mL for doses from 200 µg to 1200 µg | 3.46–20.43 ng·h/mL for doses from 200 µg to 1200 µg | Approximately 14 hours (terminal $t_{y}$·) |
| Sublingual fentanyl tablet (Abstral[f])<br>100 µg, 200 µg,<br>300 µg, 400 µg,<br>600 µg, 800 µg | 54% | NA | 30–60 Minutes (range: 16–240 minutes) for doses from 100 µg to 800 µg | 0.187–1.42 ng/mL for doses from 100 µg to 800 µg | 0.974–8.95 ng·h/mL for doses from 100 µg to 800 µg | 5.02–10.1 Hours for doses from 100 µg to 800 µg |
| Sublingual fentanyl spray (Subsys[g])<br>100 µg, 200 µg<br>400 µg, 600 µg<br>800 µg | 76% | NA | 0.69–1.25 hours (range: 0.08–4.00 hours) for doses from 100 µg to 800 µg | 0.20–1.61 ng/mL for doses from 100 µg to 800 µg | 1.25–10.38 ng·h/mL for doses from 100 µg to 800 µg | 5.25–11.99 Hours for doses from 100 µg to 800 µg |
| Intranasal fentanyl spray (Instanyl[h])<br>50 µg, 100 µg<br>200 µg | 89% | Not relevant | 12–15 Minutes for doses from 50 µg to 200 µg | 0.35–1.2 ng/mL for doses from 50 µg to 200 µg | NA | Elimination $t_{y}$· 3–4 hours |
| Fentanyl pectin nasal spray (Lazanda[i])<br>100 µg, 400 µg<br>(enabling dosing at<br>100 µg, 200 µg,<br>400 µg, and 800 µg) | NA; prescribing information states that bioavailability is 120% of that for oral transmucosal fentanyl citrate | NA | 0.33–0.35 hours for doses from 100 µg to 800 µg | 351.5–2844.0 pg/mL for doses from 100 µg to 800 µg | 2460.5–17,272 ng·h/mL for doses from 100 µg to 800 µg | 15–24.9 Hours for doses from 100 µg to 800 µg |

[a] Reproduced with permission from Smith, 2013[68].
[b] Currently, only Fentora and Abstral are approved by Health Canada.
[c] Unless otherwise stated.
[d] Cephalon, Malvern, PA, U.S.A.
[e] BioDelivery Sciences, Raleigh, NC, U.S.A.
[f] Sentynl Therapeutics, Solana Beach, CA, U.S.A.
[g] INSYS Therapeutics, Phoenix, AZ, U.S.A.
[h] Takeda Pharmaceuticals International, Zurich, Switzerland.
[i] Depomed, Newark, CA, U.S.A.

$T_{max}$ = time taken to reach $C_{max}$; $C_{max}$ = maximum plasma drug concentration; $AUC_{0-\infty}$ = area under the plasma concentration–time curve from time zero to infinity; $t_{\cdot}$ = half-life; NA = not available.

populations studied and the trial designs. In the absence of clear data about the relative efficacy of the products, prescribing decisions can be based on the advantages and disadvantages of the various routes of administration. A recent review of the pharmacokinetic profile of transmucosal fentanyl formulations revealed 3 different concentration profiles (Figure 4)[70]:

- Very rapid rise and short duration (with intranasal administration)
- Rapid increase and sustained intensity (with buccal delivery)
- Slower onset and longer duration

Thus, the choice in the clinic might be driven by the pain syndrome experienced by the patient. For example, for very-rapid-onset and short-duration pain, a product with a rapid rise in concentration might be beneficial, while a rapid-but-sustained concentration profile appears to be more suitable for pain with fast onset but prolonged duration. For pain with a slower onset and longer duration, the review suggests consideration of the slower-and-longer profile achieved with oral transmucosal fentanyl citrate. However, the latter formulation is not available in Canada.

Although current guidelines vary in their methodology, rigour, and expert working group composition, they all include the use of rapid-onset opioids (transmucosal fentanyl formulations) tailored to the unique BTcP presentation[71–74]. The inclusion of fentanyl transmucosal formulations in the present guideline is based on two recent meta-analyses that favoured that approach over the traditional ones[74,75].

### Consensus Points

- Two recent meta-analyses indicate the benefits of transmucosal fentanyl formulations over traditional approaches, especially when treating pain that has rapid onset and short duration.

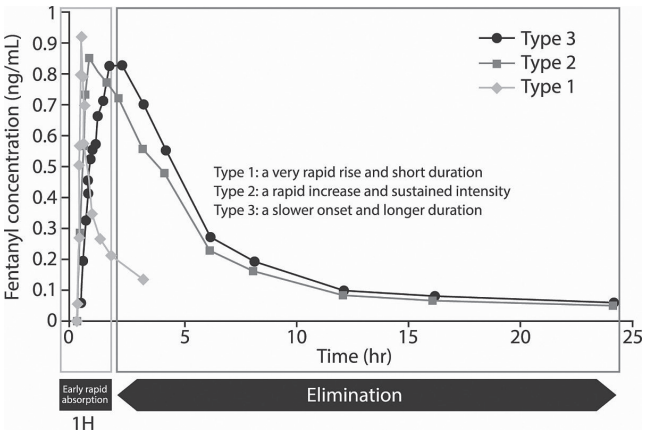


**FIGURE 4** Pharmacokinetic profile of transmucosal fentanyl formulations. Reproduced with permission from Moore *et al.,* 2012[70].

- The pharmacokinetics or pharmacodynamics of the 3 available fentanyl formulations should be taken into consideration when deciding on the therapeutic approach for a specific type of BTcP. The pharmacologic properties of the fentanyl formulation should be matched with the characteristics of the BTcP, including its onset and duration.
- Transmucosal fentanyl formulations should never be used in opioid-naïve patients.
- To assess the effectiveness of the selected approach for the management of BTcP, the same assessment tools or scale should be used both before and after treatment.

### Education Point

- Additional efforts are required to build awareness among health care professionals, especially pharmacists, that the various new formulations of transmucosal fentanyl are not equianalgesic and are therefore not interchangeable.

## MANAGEMENT OF BTcP: CANADIAN PERSPECTIVE

In Canada, the most common approach to the management of BTcP includes the use of the traditional short-acting opioids (morphine, hydromorphone, oxycodone). Currently, two new transmucosal fentanyl products, administered sublingually (Abstral: Sentynl Therapeutics, Solana Beach, CA, U.S.A.) or buccally (Fentora: Cephalon, Malvern, PA, U.S.A.), are approved by Health Canada[55]. The dosing and titration process required with the new products often presents challenges for both the patient and the health care provider, because the initially chosen dose is often inadequate to control the pain and rescue medication has to be taken. A higher transmucosal fentanyl dose is then used for future breakthrough episodes, but it cannot be taken until after 4 hours have passed. Titration usually takes 1–2 days and often requires regular contact with the patient for reassurance and advice. Some investigators challenge this titration principle, especially for patients taking a higher background opioid dose, because those patients also need higher background doses[76]. However, data to recommend a proportional-dose approach are limited.

Several current provincial guidelines for the management of cancer pain in Canada include a brief discussion on the treatment of BTcP[77–79], but no uniform recommendations for the management of BTcP have been made at the national level. That lack of a national recommendation, together with the unequal access to pain medication across the country, contributes to regional and provincial variability in the management of BTcP. Furthermore, although immediate-release morphine, hydromorphone, and oxycodone are recommended by the Canadian Agency for Drugs and Technologies in Health's Common Drug Review and are listed on most provincial formularies, transmucosal fentanyl formulations are not recommended, and access to those agents is limited. Higher costs of transmucosal fentanyl formulations compared with other available oral opioids, together with a lack of direct comparisons, are the

main reasons for unfavourable recommendations. In addition, the Canadian Drug Expert Committee stated that the abuse potential with these agents is also considerable.

Because of a lack of access to one of the approved transmucosal fentanyl formulations, many Canadian hospitals use an off-label sublingual or injectable sufentanil[55]. An oral syringe or a spray bottle is used to deposit the sufentanil under the tongue. This relatively inexpensive method is complicated in terms of preparation and consistency of dosing, and its use should be limited to palliative care units.

Another frequent approach is the off-label use of intranasal injectable fentanyl or sufentanil (or both) through a Mucosal Atomization Device (Teleflex, Morrisville, NC, U.S.A.)[80]. The ideal volume for intranasal administration is 0.2–0.3 mL, because volumes above 0.5 mL will not be well absorbed, tending to drip down the back of the throat and be swallowed. In certain patients, the use of sufentanil is therefore recommended.

A recent study in the province of Quebec that used the Régie de l'assurance maladie du Québec database revealed that, in a cohort of 48,420 people dying of cancer, almost 60% did not fill their community-based opioid prescriptions on a regular basis. On the other hand, in patients who did fill their prescriptions, the opioid dose tended to increase significantly over time (Figure 5). That observation might be the result of increased pain because of disease progression, development of opioid tolerance, or the attempt by clinicians to treat BTCP by increasing the dose of background opioids. Assessment of the development of opioid tolerance in cancer patients is somewhat difficult in clinical practice because of an inability to distinguish whether the increasing opioid requirement is the result of disease progression, a true pharmacologic tolerance, or opioid-associated hyperalgesia.

It is also interesting to note that the first prescriber of opioids for cancer patients in Canada is the family physician (37% of cases), followed by the medical oncologist (19%)[17]. However, adjustments in the opioid prescription are more likely to be made by oncology staff. A recent survey also revealed that the most commonly used opioid for background cancer pain in Canada is hydromorphone (26%), followed by oxycodone (19%), morphine (14%), and fentanyl (14%)[17]. Hydromorphone (37%) and morphine (22%) are also the drugs most commonly used for breakthrough pain. The survey also indicated the need for more effective and faster-acting pain relief medications; only 37% of patients indicated that they were satisfied with the speed of pain relief, and only 19% indicated very good level of relief. When asked to specify the most important features of a new treatment for breakthrough pain, 47% of patients indicated the ability to relieve pain completely, and 43% highlighted the ability to relieve pain quickly. Of every 5 patients, 4 (80%) said that they were willing to try transmucosal products.

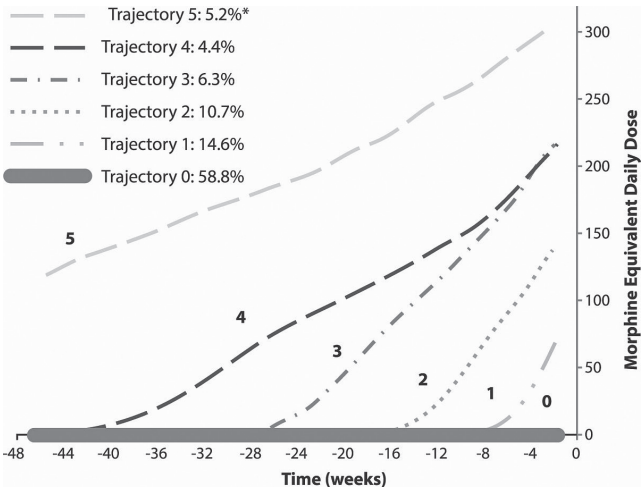


**FIGURE 5** Patterns of community-based opioid prescription filling in people dying of cancer during their last 11 months of life in the province of Quebec. Reproduced with permission from Gagnon *et al.,* 2015[81].

## Consensus Point

- Although injectable fentanyl and sufentanil are used sublingually or intranasally off-label in the hospital setting, where trained personnel can administer them, this practice is not recommended for out-of-hospital settings. Only tested applications should be used in home and hospice settings, especially given that approved and safe drug delivery systems are available. Clinicians should keep in mind that fentanyl is absorbed quickly and that the time to maximum plasma concentration can be very rapid. Serious consequences can ensue during off-label use by inexperienced health care professionals or in an inappropriate setting.
- When assessing the abuse potential for either long- or short-acting opioids, the treating clinician should keep in mind that all opioids have the potential to activate the reward system in the brain. Although the pharmacology and the mechanism of action of fentanyl meet all criteria for potential to abuse, there is no evidence that transmucosal formulations are more addictive. Nasal administration might be more challenging, because patients and caregivers might not be certain whether the appropriate dose has been given.
- Concerns related to opioid abuse and dependence should not prevent clinicians from using opioids in patients who have only a few months to live. Making such patients as comfortable as possible should be the top priority.

## Education Points

- Fear of opioid use is an ongoing issue, because addiction- and abuse-related concerns lead to continued reluctance on the part of many clinicians to prescribe opioids. Thus, additional education efforts and initiatives are needed to lessen such concerns so that cancer patients are provided with adequate pain control.
- Additional efforts are needed to identify the true reasons for the continuous increase in opioid dose in end-of-life cancer patients. If the increase in dose is indeed related to attempts by clinicians to control breakthrough pain, then education initiatives about alternative options, including use of the short-acting fentanyl formulations, are needed.

## SUMMARY

Management of BTCP remains a balancing act. It is influenced by the nature of pain itself, but also by access to therapies, fear of addiction, and medication tolerance. When assessing BTCP, the cause of the baseline pain has to be taken into consideration. Management considerations for BTCP depend on its pathophysiology, the setting in which the patient is treated, and the stage of the disease.

The traditional use of oral opioid formulations and the use of newer transmucosal fentanyl formulation are both valid options, provided that background pain is adequately controlled and that treatment of BTCP is individualized according to patient needs and the unique characteristics of the pain episodes.

### Consensus Recommendations

- The medical community has to be aware that BTCP is a prevalent condition with detrimental consequences for patients, caregivers, and the health care system.
- The first step in diagnosing and treating BTCP is to ensure that background pain is properly addressed. The experience of pain in cancer patients is multifactorial and varies from patient to patient. Clinicians have to recognize and differentiate between neuropathic and other types of cancer pain so as to select proper therapy.
- Clinicians should be aware of the two recently developed assessment tools for BTCP that can be used in specific complicated situations with challenging diagnoses. However, for daily routine practice, simpler tools and scales such as the diagnostic algorithm proposed by Davies *et al.*[4] and a NRS are recommended.
- Clinicians should strive to identify and treat all underlying causes of pain, regardless of whether the pain is predictable or unpredictable. Some types of pain are unpredictable despite the fact that a trigger (coughing, for instance) is identifiable. In such cases, clinicians should treat the causative event (that is, the cough).
- Breakthrough cancer pain can be effectively managed with immediate-release oral opioids or with transmucosal fentanyl preparations.
- For some types of BTCP, transmucosal fentanyl formulations are preferable to immediate-release oral opioids because of more rapid onset of action and shorter duration of effect.
- The cost of transmucosal fentanyl preparations should not impede their use, especially taking into consideration that many patients in need of those medications have a very short life expectancy and that the medication will be needed for only a brief period of time. Policymakers should keep those factors in mind when making their listing recommendations.
- As for all opioids, the risks of addiction and diversion should be taken into consideration, and appropriate assessment and monitoring should be applied. Again, addiction concerns should not prevent clinicians from using opioids in patients who have only few months to live.

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#### CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: In addition to participation in the meeting, PD reported receiving honoraria from Tweed (speaker fees), Prairie Plant Systems (education advisory board), and Bonify (scientific advisory board), and RG reported receiving honoraria from Purdue Pharma (education events). BG is a recipient of a Chercheur–clinicien Boursier award from the Fonds de recherche du Québec–Santé. The other meeting participants declare that they have no conflicts to report.

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