Pharmacologic management of adult breakthrough cancer pain

Bruce Doulton MD CCFP

The generally accepted current definition of *breakthrough cancer pain* (BTCP) is as follows: "a transient exacerbation of pain that occurs either spontaneously, or in relation to a specific and predictable or unpredictable trigger, despite relatively stable and adequately controlled background pain."[1] Spontaneous pain is also referred to as *idiopathic pain*. Triggers are also referred to as *incidents* or *incident pain.* The triggers can be a volitional act (eg, walking), nonvolitional act (eg, coughing), or procedural act (eg, dressing change).[2] *End-of-dose failure* refers to medication wearing off before the next regular analgesic dose is due and is no longer considered a subset of BTCP. The causes of BTCP include the cancer itself, cancer treatment side effects, and comorbidities. A recent systematic review found that 1 in 2 patients with cancer pain experience BTCP.[3] There have been a number of attempts to develop assessment tools for BTCP. A recently developed and validated breakthrough pain assessment tool by Webber et al[4] is available at **CFPlus**.*

Breakthrough cancer pain contributes substantially to the suffering experienced by cancer patients,[5-7] affecting patients' quality of life. Patients often have problems with movement, which prompts avoidance and results in a number of associated complications including joint stiffness, muscle wasting, pressure sores, and constipation. Difficulty completing activities of daily living prompts reliance on family members and health agencies. Psychological complications include mood disturbances, problems with interpersonal relationships, and a general lack of enjoyment of life.

Unfortunately, BTCP is not always adequately managed; the reasons for this include limited use of nonpharmacologic treatments (eg, heat, ice, distraction, imagery, massage, transcutaneous electrical nerve stimulation), patient fear of medication addiction and tolerance, and patient dissatisfaction with medication effectiveness and side effects. Other reasons that are related to the availability of newer management options include difficulty matching the appropriate medication with the particular type of BTCP, availability and cost of newer treatments, and the lack of familiarity with these new treatments among patients and health care providers. Management of BTCP includes treating the underlying cause of the pain, avoiding or treating factors that precipitate the pain, modifying the background drug regimen, and using appropriate adjuvants and breakthrough medications. This article will focus on the latter. Pain "crisis" will not be addressed in this article (it is best managed in the inpatient setting with intravenous medications).

The pharmacologic options for management of BTCP have increased considerably in the past decade. The prime stimulus for these new products is the management of a particular subset of BTCP, which has a fast onset and short duration and is often intense. Most of these new options are fentanyl based owing to the highly lipophilic nature of fentanyl, allowing for transmucosal absorption (sublingual, buccal, intranasal). Fast-acting fentanyl products are commonly referred to as *rapid-onset opioids* (ROOs). In the United States, they are often called *transmucosal immediate-release fentanyl* drugs.

In Canada most BTCP cases are managed with only the traditional short-acting opioids (SAOs) (ie, morphine, hydromorphone, and oxycodone). Currently, there are 2 new fentanyl citrate products (administered sublingually or buccally) that have been approved and are available in Canada.[8,9] An off-label option used in some centres is injectable fentanyl and sufentanil, administered sublingually rather than by injection.

Traditional management

When the stable opioid dose for control of the background pain has been determined, the breakthrough dose is calculated. Typically, 5% to 20% (usually 10%) of the total daily analgesic dose is used as a guideline for determining the appropriate initial breakthrough dose, and this is given every hour as needed orally or every 30 minutes as needed in a subcutaneous equivalent. Another method of calculating the breakthrough dose is 50% of the every-4-hour dose (whether orally or subcutaneously). If the background dose is increased, then the breakthrough dose has to be increased accordingly.

The same medication that is used for control of the background pain is typically used as an SAO for the

La traduction en français de cet article se trouve à **www.cfp.ca** dans la table des matières du numéro **de décembre 2014** à la **page e585.**

*A breakthrough pain assessment tool is available at **www.cfp.ca.** Go to the full text of the article online and click on **CFPlus i**n the menu at the top right-hand side of the page.

breakthrough pain. The common exception to this is with the use of the fentanyl transdermal patch because administering fentanyl orally is not effective and subcutaneous and transmucosal routes for fentanyl use have traditionally been limited. Usually the choice of short-acting morphine, oxycodone, or hydromorphone depends on the particular clinical situation. Approximate breakthrough doses for the fentanyl transdermal patch are shown in **Table 1**.[10]

For predictable BTCP (eg, dressing change or other procedure), the traditional SAO is given in advance (45 to 60 minutes for oral administration; 30 minutes for subcutaneous route). The *Palliative Care Formulary* editions provide further details on traditional approaches.[11,12]

Using injectable fentanyl or sufentanil sublingually

It should be stressed that injectable fentanyl or sufentanil administered sublingually is an off-label use of these products. This option is chosen in some Canadian centres when fast-onset analgesia with short duration of action is desired but the new ROOs are not available or are believed to be too costly. The focus of the use of these medications has been predictable triggers (eg, procedures). Onset of analgesic effect is 5 to 10 minutes.[13] There are no studies that compare this option directly with any of the new ROOs.

These are very potent medications and should be handled with care. A 10-mg dose of subcutaneous morphine, a 100-µg dose of fentanyl, and a 10-µg dose of sufentanil are approximate equivalent doses (ie, sufentanil is approximately 10 times more potent than fentanyl is). These approximate equivalent doses are for information purposes only; this information is not intended to be solely used when rotating one product to another, as incomplete cross-tolerance has to be considered.

For administering injectable fentanyl sublingually, an oral syringe or a spray bottle is used to deliver doses of 25 to 50 µg. The solution must be held in the mouth for 2 minutes. If necessary, the fentanyl dose is increased to between 50 and 100 µg; many patients do not need more than this. Fentanyl doses greater than 100 µg are impractical because 2 mL is the maximum volume that can be reliably kept in the mouth for transmucosal absorption.[12] For higher doses, consider switching to sufentanil or alfentanil.

An alternative approach is to restrict the use of injectable fentanyl to only those patients who take low-dose opioids and use sufentanil in those patients who take higher doses.[10] The starting sufentanil dose is 6.25 to 12.5 µg. The peak analgesic effect of sufentanil occurs within 15 to 30 minutes and its duration of effect is 30 to 40 minutes. Sufentanil injection should be given 10 to 15 minutes in advance for incident pain control.

Table 1. Approximate breakthrough doses recommended for the fentanyl transdermal patch

PATCH STRENGTH, µg/h	ORAL MORPHINE IR, mg	ORAL HYDROMORPHONE IR, mg	ORAL OXYCODONE IR, mg
12	5	1	2.5-5
25	10	2	5-7.5
50	20	4	10-15
75	30	6	16-25
100	40	8	20-30

IR—immediate release.
Data from Fraser Health.[10]

Rapid-onset opioids

Rapid-onset opioids are highly lipid-soluble, pure µ-opioid agonists. They were developed specifically for breakthrough pain that is rapidly escalating and of short duration (<60 minutes) (eg, when a patient with bony metastasis is walking). The onset of analgesia for SAOs is typically 30 to 45 minutes, while for the ROOs it is 5 to 15 minutes. The SAOs often last longer than the pain episode, which results in sedation. Patients often avoid SAOs because of slow onset and prolonged duration and would rather "just put up with the pain."

The ROOs are approved only for treatment of cancer pain and only for those cancer patients who are considered to be opioid tolerant. These are patients who take background opioid doses of at least 60 mg of oral morphine daily, at least 25 µg of transdermal fentanyl per hour, at least 30 mg of oral oxycodone daily, at least 8 mg of oral hydromorphone daily, or an equivalent dose of another opioid daily for 1 week or longer.

The dosing schedule for ROOs is a challenge for both the patient and the provider. The goal is adequate analgesia with minimal adverse effects. The guiding principle is that the background (basal) analgesic does not predict the BTCP dose. This means that the doses are titrated for all the ROOs and are *not* proportional to the background dose. This can be initially frustrating until the optimum dose is determined. Sometimes the initial dose chosen is inadequate to control the pain and an SAO has to be added. A higher ROO dose is then used for future breakthrough episodes. The ROO cannot be repeated until 4 hours after the SAO. Titration usually takes 24 to 48 hours and often necessitates regular contact with the patient for reassurance and advice. The maximum number of effective ROO treatments for BTCP in 24 hours is generally 4. If more treatments are required, then the background dose should be increased.

Some authorities challenge this titration principle, especially for those taking a higher background opioid dose.[14] They note that those taking higher background doses tend to need higher breakthrough doses.

However, there are not enough data to recommend a proportional-dose approach.

The side effect profile is typical of all opioids (sedation, somnolence, nausea, vomiting, constipation, dry mouth, fatigue, respiratory depression, etc). All ROOs also have particular local adverse effects. The ROOs are not interchangeable. The titration schedule has to be repeated if the ROO is changed. Some ROOs can be swallowed, which might give a longer-than-expected duration of effect.

Fentanyl is primarily metabolized in the liver by the enzyme cytochrome P450 3A4. Medications that inhibit this enzyme can increase the fentanyl levels and might result in sedation, other adverse effects, and fatal overdose. A partial list of inhibitors for this enzyme includes the macrolide antibiotics, azole antifungals, certain protease inhibitors (eg, ritonavir, indinavir), verapamil, aprepitant, diazepam, hydroxyzine, selective serotonin reuptake inhibitors, venlafaxine, and grapefruit juice. Medications that induce this enzyme can decrease the fentanyl levels and decrease its effectiveness. Care must be taken in starting or stopping these inducers. A partial list of inducers for this enzyme includes carbamazepine, dexamethasone, phenobarbital, phenytoin, rifampin, modafinil, and St John's wort.

Rapid-onset opioids are highly potent opioids. They must be handled safely and dosed appropriately, and the risks of diversion and poisoning must be considered. Rapid-onset opioids can be fatal to children. The Transmucosal Immediate Release Fentanyl Risk Evaluation and Mitigation Strategy program in the United States provides risk management plans for the serious risks associated with ROOs.[15] Patients, pharmacists, and prescribers all must complete educational materials and registries provided for these products. A similar national program does not exist in Canada.

Table 2[8,9,16] shows a list of internationally approved ROOs. Although buccal soluble film had been previously approved in Canada and the United States, it was withdrawn mainly because of problems associated with the manufacturing process. (It is available in the United Kingdom.) Taylor[17] and the *Palliative Care Formulary*[11] provide more in-depth reviews of internationally available ROOs.

Table 2. Fentanyl-based rapid-onset opioids available worldwide

DRUG FORMULATION	DOSES, µg	AVAILABILITY
Buccal or sublingual tablet[9]	100, 200, 400, 600, 800	Canada, United States
Sublingual tablet[8,16]	100, 200, 300, 400, 600, 800	Canada, United States
Oral transmucosal lozenge on a stick	200, 400, 600, 800, 1200, 1600	United States
Pectin-based nasal spray	100, 400	Unites States, European Union
Buccal soluble film	200, 400, 600, 800, 1200	European Union
Sublingual spray	100, 200, 400, 600, 800, 1200, 1600	United States
Nasal spray	50, 100, 200	European Union

Discussion

There is limited evidence comparing the various options for treating BTCP. Most of the studies examining the effectiveness of ROOs compare them with placebo.[18,19] There are no head-to-head studies comparing the ROOs.[20-22] In a recent "indirect" comparison study, Zeppetella et al found that the ROOs achieved a greater level of pain relief in a shorter period of time than placebo or oral morphine did.[23,24]

International guidelines addressing the use of ROOs have been inconsistent. The European Association of Palliative Care recommends ROOs as the treatment of choice for BTCP. The National Institute for Health and Clinical Excellence recommends not to deliver ROOs in BTCP before a trial of an oral SAO.[25]

Much of the debate concerning the use of ROOs has revolved around the issue of cost.[26,27] Approximate costs per dose for some of the options are as follows: less than $1 for typical oral morphine and hydromorphone; $4 for injectable fentanyl (50 µg/mL, 2 mL); $11 for all strengths of fentanyl buccal or sublingual effervescent tablets; and $11 to $28 for fentanyl citrate sublingual tablets, depending on strength. Both the fentanyl products available in Canada[8,9] are covered by some private insurers, but neither product is covered on any of the provincial formularies. It remains to be seen whether ROOs will be included on provincial or hospital formularies or whether the use of these new products in Canada will be restricted to those in clinical studies, those who have private insurance, or those who are personally able to pay for them.

Short-acting opioids remain the initial treatment of choice for most BTCP, especially for pain that is slow onset to peak intensity. For BTCP that is fast onset and of short duration, injectable fentanyl (or sufentanil) administered sublingually should at least be considered. For those patients or health agencies that can afford them, ROOs are the agents of choice for fast-acting, short-duration BTCP control.

Dr Doulton practises family medicine and palliative care in St John's, Nfld.

Acknowledgment

I thank **Dr Lisa Bishop** from the School of Pharmacy at Memorial University of Newfoundland in St John's for her help in collecting some of the information presented.

Competing interests

None declared

References

1. Davies AN. Breakthrough cancer pain. *Curr Pain Headache Rep* 2014;18(6):420.
2. Wengström Y, Geerling J, Rustøen T. European Oncology Nursing Society breakthrough cancer pain guidelines. *Eur J Oncol Nurs* 2014;18(2):127-31. Epub 2013 Dec 24.

3. Deandrea S, Corli O, Consonni D, Villani W, Greco MT, Apolone G. Prevalence of breakthrough cancer pain: a systematic review and a pooled analysis of published literature. *J Pain Symptom Manage* 2014;47(1):57-76. Epub 2013 Jun 21.
4. Webber K, Davies AN, Zeppetella G, Cowie MR. Development and validation of the breakthrough pain assessment tool (BAT) in cancer patients. *J Pain Symptom Manage* 2014;48(4):619-31. Epub 2014 Apr 22.
5. Bedard G, Hawley P, Zhang L, Slaven M, Gagnon P, Bisland S, et al. A survey of Canadian cancer patients' perspectives on the characteristics and treatment of breakthrough pain. *Support Care Cancer* 2013;21(9):2557-63. Epub 2013 May 2.
6. Buchanan A, Davies A. Breakthrough cancer pain: the current situation. *Int J Palliat Nurs* 2014;20(1):6-8.
7. Davies A, Buchanan A, Zeppetella G, Porta-Sales J, Likar R, Weismayr W, et al. Breakthrough cancer pain: an observational study of 1000 European oncology patients. *J Pain Symptom Manage* 2013;46(5):619-28. Epub 2013 Mar 22.
8. Paladin Labs Inc. *Abstral. Fentanyl citrate sublingual tablets* [product monograph]. Montreal, QC: Paladin Labs Inc; 2012.
9. Teva Canada Ltd. *Fentora. Fentanyl buccal/sublingual effervescent tablets* [product monograph]. Toronto, ON: Teva Canada Ltd; 2013.
10. Fraser Health [website]. *Hospice palliative care symptom guidelines*. Surrey, BC: Fraser Health; 2012. Available from: **http://fraserhealth.ca/EN/hospice_palliative_care_symptom_guidelines.** Accessed 2014 Oct 29.
11. Palliativedrugs.com. *Palliative care formulary.* 5th ed. Nottingham, UK: Palliativedrugs.com; 2014.
12. Twycross R, Wilcock A, Dean M, Kennedy B. *Palliative care formulary.* Canadian ed. Nottingham, UK: Palliativedrugs.com; 2014.
13. Gardner-Nix J. Oral transmucosal fentanyl and sufentanil for incident pain. *J Pain Symptom Manage* 2001;22(2):627-30.
14. Mercadante S, Prestia G, Casuccio A. The use of sublingual fentanyl for breakthrough pain by using doses proportional to opioid basal regimen. *Curr Med Res Opin* 2013;29(11):1527-32. Epub 2013 Aug 19. Erratum in: *Curr Med Res Opin* 2014;30(3):527.
15. Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy [website]. Phoenix, AZ: TIRF REMS Access. Available from: **www.tirfremsaccess.com/TirfUI/rems/home.action**. Accessed 2014 Nov 4.
16. Canadian Pharmacist's Letter [website]. *Abstral (fentanyl) sublingual tablets*. Stockton, CA: Therapeutic Research Center; 2014.
17. Taylor DR. *Managing cancer breakthrough pain*. New York, NY: Springer Healthcare; 2013.
18. Slatkin NE, Xie F, Messina J, Segal TJ. Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. *J Supportive Oncol* 2007;5(7):327-34.
19. Portenoy RK, Taylor D, Messina J, Tremmel L. A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. *Clin J Pain* 2006;22(9):805-11.
20. Mercadante S. Managing difficult pain conditions in the cancer patient. *Curr Pain Headache Rep* 2014;18(2):395.
21. McWilliams K, Fallon M. Fast-acting fentanyl preparations and pain management. *QJM* 2013;106(10):887-90. Epub 2013 Apr 22.
22. Elsner F, Zeppetella G, Porta-Sales J, Tagarro I. Newer generation fentanyl transmucosal products for breakthrough pain in opioid-tolerant cancer patients. *Clin Drug Investig* 2011;31(9):605-18.
23. Zeppetella G, Davies A, Eijgelshoven I, Jansen JP. A network meta-analysis of the efficacy of opioid analgesics for the management of breakthrough cancer pain episodes. *J Pain Symptom Manage* 2014;47(4):772-85. Epub 2013 Aug 24.
24. Meijler WJ. Reply: a network meta-analysis of the efficacy of opioid analgesics for the management of breakthrough cancer pain episodes. *J Pain Symptom Manage* 2014;47(6):e9-10. Epub 2014 Mar 28.
25. Gaertner J, Schiessl C. Cancer pain management: what's new? *Curr Pain Headache Rep* 2013;17(4):328.
26. Davis M. Are there cost benefits to fentanyl for breakthrough pain? *J Pain Symptom Manage* 2012;44(3):e1-2.
27. Kuo KL, Saokaew S, Stenehjem DD. The pharmacoeconomics of breakthrough cancer pain. *J Pain Palliat Care Pharmacother* 2013;27(2):167-75. Epub 2013 May 20.

Resources for further reading

Taylor DR. *Managing cancer breakthrough pain*. New York, NY: Springer Healthcare; 2013.

Palliativedrugs.com. *Palliative care formulary.* 5th ed. Nottingham, UK: Palliativedrugs.com; 2014.

Twycross R, Wilcock A, Dean M, Kennedy B. *Palliative care formulary.* Canadian ed. Nottingham, UK: Palliativedrugs.com; 2014.

Pallium Canada. *The pallium palliative pocketbook*. Ottawa, ON: Pallium Canada; 2013.

BOTTOM LINE

- Breakthrough cancer pain (BTCP) is not always adequately managed; some of the reasons for this include difficulty matching the appropriate medication with the particular type of BTCP, availability and cost of newer treatments, and the lack of familiarity with these new treatments among patients and health care providers.
- Management of BTCP includes treating the underlying cause of the pain, avoiding or treating factors that precipitate the pain, modifying the background drug regimen, and using appropriate adjuvants and breakthrough medications.
- Most of the new options for treating BTCP are fentanyl based. Fast-acting fentanyl products are commonly referred to as *rapid-onset opioids*. Short-acting opioids remain the initial treatment of choice for most BTCP, especially for pain that is slow onset to peak intensity. For BTCP that is fast onset and of short duration, injectable fentanyl (or sufentanil) administered sublingually rather than by injection could be considered. For those patients or health agencies that can afford them, rapid-onset opioids are the agents of choice for fast-acting, short duration BTCP control.

Palliative Care Files is a quarterly series in *Canadian Family Physician* written by members of the Palliative Care Committee of the College of Family Physicians of Canada. The series explores common situations experienced by family physicians doing palliative care as part of their primary care practice. Please send any ideas for future articles to **palliative_care@cfpc.ca.**