Abstract: Breakthrough pain (BTP) management is an unmet clinical need. BTP is poorly diagnosed, rarely evaluated and inadequately treated. BTP is transitory exacerbation of pain experienced by the patient who has relatively stable and adequately controlled baseline pain. BTP is reported to be common in adults and children with cancer as well as in non-cancer diseases associated with acute/chronic pain. Successful management of breakthrough pain depends on adequate assessment, appropriate treatment (cause of pain and symptomatic) and adequate reassessment. Ideal medication for BTP should be characterized with good efficacy and minimal side effects. Pharmacodynamic profile should mimic dynamics of BTP. Strong, short acting analgesics (e.g. opioids) administrated by route which allow quick action had potential to fulfil criteria for ideal ‘rescue’ medication for BTP. Fentanyl Buccal tablets (FBT; Fentora®, Frazer, PA, Cephalon Inc.) is novel delivery system for fentanyl citrate. FBT utilize OraVescent (r) technology to improve bioavailability and speed of transmucosal delivery. Alternate routes of administration could further improve efficacy of BTP management. Intranasal and intrapulmonary routes are under exploration. Recently introduced new delivery systems for opioids medication do represent an improvements in BTP management, however BTP is still a major challenge to pain and palliative physicians.

Keywords: cancer pain, breakthrough pain, opioids, analgesia, fentanyl buccal tablets
Introduction
Breakthrough pain (BTP) remains on of the most challenging clinical problems for physicians and patients alike. It is poorly diagnosed, rarely evaluated and inadequately treated. BTP is reported to be common in adults and children with cancer as well as in non-cancer syndromes associated with acute/chronic pain. Currently there is growing interest in BTP management generated by a greater awareness of the problem of breakthrough pain (secondary to improvement in the management of background pain) as well as its significant negative impact on quality of life, and fuelled by an increasing range of pharmacological options for the treatment of breakthrough pain. BTP has a significant negative impact on quality of life. Complications of BTP are summarized in Table 1.

Definition of BTP
BTP is a transitory exacerbation of pain experienced by a patient who has relatively stable and adequately controlled baseline pain. Bennett proposed a similar definition: BTP is an abrupt, short lived and intense pain that ‘breaks through’ the around the clock analgesia that controls persistent pain. Other names include: episodic pain, exacerbation of pain, pain flare, transient pain, transitory pain. The Expert Working Group of the European Association for Palliative Care (EAPC) has suggested that the term ‘breakthrough pain’ should be replaced by the terms ‘episodic pain’ or ‘transitory pain’. Common clinical features of BTP are summarized in Table 2.

Classification of BTP
Classification of BTP is presented in Table 3 (modified from). End-of dose failure is not a subtype of breakthrough pain it should rather be simply classified as inadequately controlled pain. Patients with no background pain but who have severe episodic bouts of pain are classified as having transitory pain and patients with poorly controlled background pain with or without severe transitory episodic exacerbations of pain are classified as having uncontrolled pain.

Prevalence of BTP
In a recent international survey, clinicians reported BTP in 23%–90% of adult cancer patients, and 74% in opioids treated non-cancer pain patients. BTP appears to be more common in patients with advance disease. In majority of studies the prevalence of incident related BTP (range 43%–64%) was higher than the prevalence of spontaneous BTP (relevance range: 17%–38%). Only one study observed opposite prevalence (spontaneous 59%, incident 24%). Prevalence of BTP varies between different groups of patients and is affected by certain language/geographical variables. BTP is a poor prognostic indicator.

Assessment of BTP
Breakthrough pain is not a single entity, but a spectrum of very different entities. The clinical features vary from individual to individual, and may vary within individuals over time. Table 4 summarizes diagnostic criteria for BTP. Successful management of breakthrough pain depends on adequate assessment (Table 5), appropriate treatment (cause of pain and symptomatic) and adequate reassessment. Many patients have more than one type of breakthrough pain and an association between the presence of breakthrough pain and the intensity/frequency of the background pain has been reported. Circadian variation in the occurrence of BTP has been reported (86% patients experienced BTP during day and only 45% during night). Formal assessment tools for BTP are presented in Table 6.

Treatments of BTP
Holistic/multimodal approaches for BTP treatment have been proposed. Principles of BTP management

Table 1. Breakthrough pain could lead to following complications.
- Physical (decreased functioning)—predominantly due to mobilizing difficulty and sleep disturbances
- Psychological—predominantly mood disturbances, anxiety and depression
- Social—predominantly due to movement related pain
- Economical—BTP is associated with increased use of health care services (e.g. longer stays in hospital) which lead to an increase in costs for the health service, patient and their carers
Breakthrough pain

Table 2. Common clinical features of breakthrough pain.

- Frequent in occurrence
- Acute in onset
- Short in duration
- Moderate to severe in intensity
- Related to background pain

Table 3. Classification of breakthrough pain.

- Spontaneous pain (idiopathic pain)—pain occurs unexpectedly
- Incident pain (precipitated pain)—pain related to specific event*
  - Volitional incident pain—precipitated by voluntary act (e.g. walking)
  - Non-volitional incident—pain precipitated by involuntary act (e.g. coughing)
  - Procedural pain—related to a therapeutical interventions (e.g. wound dressing)
- End of dose failure—due to insufficient overall dose of opioids**

*Incident pain related to movement (volitional or non-volitional) is called movement related pain.
**Often not regarded as true breakthrough pain.

Table 4. Diagnostic criteria for breakthrough pain.

- The presence of stable analgesia in the previous 48 hours
- The presence of controlled background pain in the previous 24 hours
- The presence of temporary flares of severe or excruciating pain in the previous 24 hours

Ideal ‘Rescue’ Medication for BTP

The ideal medication for BTP should be characterized by good efficacy and minimal side effects. The pharmacodynamic profile should mimic the dynamics of BTP (Table 10). A potent, short acting analgesic (e.g. opioid) administrated by a route which allows for a rapid onset of action has the potential to fulfil the criteria for an ideal ‘rescue’ medication for BTP. A new class of opioids, Rapid Onset Opioids (ROOs), has been developed in an attempt to address the “unmet need” of breakthrough pain management.

Patients on chronic intake of opioids would have developed some tolerance to opioid side effects. Since the side effects associated with taking any dose of opioids (e.g. somnolence, nausea, vomiting, and dizziness), one can infer that significant increase in the intensity of side effects from BTP medications should be less likely to occur when BTP medication is administrated to an opioid tolerant patient. This concept led to the use of these potent ROOs only in opioid tolerant patients. While only approved for use in cancer pain, the utility of ROOs for pain in opioid tolerant non-cancer pain patients has been reported.

Traditionally it has been suggested that one should use the same opioid to treat background and breakthrough pain. The current approach utilizes opioids according to their pharmacodynamic properties and their pharmacokinetics: long acting for background pain and short acting (and preferably rapid onset) for breakthrough pain. Sometimes the same opioid is used for background and BTP as when a fentanyl patch is used to treat background pain and a rapid onset buccal or nasal fentanyl (transmucosal) preparation is used to treat breakthrough pain.

Table 5. Assessment of pain.

- Onset of pain
- Temporal pattern of pain
- Site of pain
- Radiation of pain
- Quality of pain
- Intensity of pain
- Exacerbating factors
- Relieving factors
- Response to analgesics
- Response to other interventions
- Associated physical symptoms
- Associated psychological symptoms
- Interference with daily activities

are presented in Table 7. Physical, pharmacological, neuro-modulatory treatments and invasive procedures are used in BTP management (Table 8). Pharmacological management should be tailored to the type of breakthrough pain (Table 9).
Table 6. Tools for assessment of BTP.

- Breakthrough pain assessment algorithm (developed by portenoy R)
- Episodic pain documentation sheet (Zappatello 2002)
- Breakthrough pain questionnaires (Portenoy 1990) with later modifications

Table 7. Principles of BTP management.

- Implementing primary therapies (surgery, radiotherapy, chemotherapy)
- Optimising around the clock medication (long acting medication)
- Specific pharmacological interventions (short acting, ‘rescue’ medication)

Table 8. Treatment options for BTP.

- Physical
  - Rubbing/massage
  - Application of heat
  - Application of cold
  - TENS (transcutaneous electric stimulation)
  - Distraction
  - Relaxation
  - Hypnotherapy/hypnosis

- Pharmacological
  - Modification of the background analgesic regimen
    - Increase dose of analgesic
    - Using stronger analgesic
    - Opioid rotation
    - Addition of another analgesic
    - Addition of co-analgesic (predominantly: anticonvulsants, antidepressant)
  - Use of breakthrough (‘rescue’) analgesic
    - Non opioid analgesic: Paracetamol, NSAID, Ketamine, Nitrous oxide
    - Opioid analgesics: Morphine, fentanyl, diamorphine, codeine, hydrocodeine
    - Other medication (e.g. midazolam—BTP due to muscle spasm)

- Invasive procedures
  - Nerve blockade
    - Peripheral nerve blockade
    - Single injection of local anaesthetics
    - Single injection of local anaesthetics with adjuvant (e.g. corticosteroids)
    - Continuous peripheral nerve/plexus blockade
  - Neuroaxial nerve blockade
    - Epidural injection/infusion
    - Intrathecal injection/infusion
  - Surgical procedures (e.g. surgical stabilization of relevant bone(s) or use of orthotic device)

- Neuromodulatory
  - TENS
  - Spinal cord stimulation—no data available for BTP, however this technique could deliver analgesia on-demand, thus potentially could be effective for BTP
  - Accupuncture—it is postulated that acupuncture can provide acute and prolonged pain relief. There is no data about efficacy of acupuncture for BTP
used to treat BTP. At other times an opioid such as a controlled or sustained release morphine product is used for background pain and a transmucosal fentanyl is used for breakthrough pain.\textsuperscript{12}

Traditionally, it was recommended to use a fixed ratio of the total daily dose of opioids to treat the breakthrough pain.\textsuperscript{41} Randomize trials have demonstrated that there is no correlation between the dose of opioid needed to control background pain and the dose of OTFC needed to control the breakthrough pain.\textsuperscript{37,42,43} Thus, the dose of breakthrough pain medication should be titrated in the same manner as dose of background medication.\textsuperscript{15} That is, the background pain medication and the BTP medication should be titrated independently. The World Health Organization (WHO) guidelines promote the use of the oral route for the management of cancer pain.\textsuperscript{44} There route has the highest patient acceptability for route of administration.\textsuperscript{45} The oral route is usually effective for the treatment of background pain; however, there are significant disadvantage of the oral route for breakthrough pain management. The oral route is associated with delayed onset of action (~20–30 minutes for oral morphine),\textsuperscript{46} delayed peak effect (~60 minute for oral morphine)\textsuperscript{15} and long duration of action (~3–6 hours).\textsuperscript{46}

Table 9. Specific treatments for different types of breakthrough pain.

<table>
<thead>
<tr>
<th>Type of Breakthrough Pain</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident pain</td>
<td>Pre-emptive use of a short acting opioid 30 minutes before activity</td>
</tr>
<tr>
<td></td>
<td>Initially use the same as the four-hourly dose of normal-release morphine (approximately 16% of the daily dose) when necessary</td>
</tr>
<tr>
<td></td>
<td>Titrate the dose of rescue medication</td>
</tr>
<tr>
<td>Idiopathic/spontaneous</td>
<td>Oral transmucosal fentanyl citrate (OTFC) was shown to be an effective treatment for breakthrough pain</td>
</tr>
</tbody>
</table>

Table 10. Features of ideal ‘rescue’ medication for breakthrough pain.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good efficacy</td>
<td></td>
</tr>
<tr>
<td>Rapid onset of action</td>
<td></td>
</tr>
<tr>
<td>Short duration of action</td>
<td></td>
</tr>
<tr>
<td>Minimal adverse effects</td>
<td></td>
</tr>
</tbody>
</table>

Advantages and disadvantages of the oral route for BTP management\textsuperscript{12,15,41,45-47} are summarized in Table 11. Alternative routes of administration was proposed: oral transmucosal\textsuperscript{15,41,42,43,48} Intravenous,\textsuperscript{49} Subcutaneous,\textsuperscript{50} Intranasal,\textsuperscript{51} and Intrapulmonary.\textsuperscript{52}

### Fentanyl Buccal Tablets

The fentanyl buccal tablet (FBT; Fentora\textsuperscript{®}, Frazer, PA, Cephalon Inc.) is a novel delivery system for fentanyl citrate. Fentanyl is a well studied, highly lipophylic, \(\mu\)-opioid agonist. The toxicological, pharmacologic effects and mechanisms of action of fentanyl are well characterized. FBT utilizes the oral transmucosal route of administration. The advantages/disadvantages of transmucosal route of administration\textsuperscript{45,53} are presented in Table 12. Transmucosal absorption allows fentanyl to bypass first-pass cytochrome P450 3A4 (CYP3A4) - mediated gastrointestinal and/or hepatic metabolism and allow more fentanyl to enter the systemic circulation compared with gastrointestinal absorption of oral fentanyl.\textsuperscript{54,55} FBT utilizes OraVescent (r) technology to improve bioavailability and speed of transmucosal delivery. At the site of administration FBT produces an effervescence reaction which causes a pH decrease followed by a pH increase. These changes of pH are hypothesized to optimize pill dissolution and membrane permeability facilitating rapid absorption.\textsuperscript{54-56}

This rapid absorption should decrease the time to onset of analgesia making FBT highly suitable for the management of breakthrough pain.\textsuperscript{57} Properties of FBT are summarized\textsuperscript{58} in Table 13. The effect of FBT has been studied out to 2 hours and analgesic effect has been shown to persist for the 2 hour study period. In studies on cancer pain FBT has demonstrated a
Table 11. Oral route for BTP ‘rescue’ medications.

- Advantages of oral route
  - Familiar/acceptable for patients and healthcare professionals
  - Convenient for patients and healthcare professionals
  - Large variety of opioid drugs and formulation available
  - Cost effective

- Disadvantages of oral route
  - Not suitable for patient suffering for
    - Dysphasia
    - Nausea
    - Vomiting
    - Dysfunction of upper gastrointestinal tract
  - Variation in oral bioavailability
  - Slow onset of action (∼20–30 minutes for oral morphine)
  - Delayed peak effect (∼60 minute for oral morphine)
  - Long duration of action (∼3–6 hours)
  - Some oral preparation contain alcohol (e.g. Oromorph oral solution 10 mg/5 ml) which makes them unsuitable for use in patients with certain religious beliefs

Table 12. Transmucosal route of administration for BTP management.

- Advantage of transmucosal route
  - Acceptable and convenient to patients
  - Acceptable to health care professionals
  - Suitable for patients which can’t use oral medications (dysphasia, vomiting, nausea, dysfunction of upper GI tract)
  - Potentially fast onset of action
  - Avoidance degradation by gastric acid and gastric enzymes
  - Avoidance of first pass metabolism
  - Cost effective than certain other (invasive) routes of administration

- Disadvantages
  - Required special formulation (OTFC, OraVescent technology)
  - Not suitable for patient with
    - Dryness of mouth
    - Oral pathology
    - Severe disability (cannot agitate the preparation)
    - Severe fatigue (cannot agitate preparation)
  - Limited number of suitable medication and formulation
  - Variation in oral transmucosal bioavailability
Table 13. Fentanyl bucal tablet.

Mechanism of action
Fentanyl is a well studied, highly lipophylic, μ-opioid agonist. The novelty of this compound is a new trans-mucosal delivery system called OraVescent®.

Pharmacokinetics
- After application fentanyl from Fentanyl Buccal Tablet (FBT) is rapidly absorbed.
- AUC0-t and Cmax are linearly proportional to dose up to dose equal 800 µg.
- Lack of bioequivalence of four 100 µg tablet with one 400 µg. Probably due to differences in tablet surface.
- Steady state is reached with 5 days for FBT 400 µg administrated every 6 hours.
- The mean ratio of the multiple dose/single dose Cmax is equal 2.0.
- Direct PK comparison of FBT vs. OTFC showed shorter Tmax (median Tmax 47 vs. 91 minute respectively) and better bioavailability: FBT = 65% vs. OTFC = 47%.

Clinical efficacy
Greater efficacy vs. placebo was proved for BTP episodes associated with cancer, low back and neuropathic pain. 65% of cancer patients, 81% of low back pain patients and 78% neuropathic pain patients were able to identify effective dose of FBT for BTP at open label titration phase.

Safety and tolerability
FBT is generally well tolerated.

Drug interaction
There is potential interaction with ritonavir. Oral ritonavir might decrease clearance of iv administrated fentanyl by 67%, resulting in 174% increase in fentanyl AUCο-∞.

Coadministration of FBT and ritonavir has not been studied, however, an increase in fentanyl AUC is expected.

15 minute onset of action. Fentanyl bucal tablets (FBT) is novel delivery system for fentanyl citrate. FBT utilises OraVescent® technology to improve bioavailability and speed of drug delivery.

Future Perspectives
Alfentanyl and Sufentanyl are the synthetic opioid analogesics, chemically similar to fentanyl but with more rapid onset and shorter duration of action when given parenterally. Sublingual Alfentanyl® and sublingual/buccal Sufentanyl® have been reported as being effective in small groups of patients for BTP treatment. Recently results of intranasal application of non-opioid medication for small group of non-cancer pain patients was published. Intranasal NMDA agonist (S)ketamine was successful in rapid reduction of neuropathic pain and may therefore be potential future medication for BTP.

Alternate routes of administration could further improve the efficacy of BTP management. Intranasal
and intrapulmonary routes are under exploration. The nose can accommodate 150–200 microliters of drug solution in each nostril. A special feature of the nasal route is the close association of the brain to the olfactory area and the unique physiology of this area (i.e. an absence of the normal blood-brain barrier): this may enable a fraction of the drug to enter the intrathecal space directly.\textsuperscript{65}

Intranasal fentanyl spray (INFS) was investigated in phase III, double blind, randomised, placebo controlled, crossover, multicenter trial. INFS was titrated to an effective dose (50, 100 or 200 microgram). Efficacy (compared with placebo) as well as safety and tolerability was demonstrated.\textsuperscript{66} INFS was also directly compared with OTFC in open-label, randomised, crossover trial. INFS demonstrated faster median time to onset of ‘meaningful’ pain relief compared to OTFC\textsuperscript{67} (Table 14). Interestingly, there was only a weak association between effective INFS doses and effective OTFC doses.\textsuperscript{67}

Several explorative studies have looked at the use of intranasal opioids for the treatment of breakthrough pain: fentanyl, morphine, diamorphine, and alfentanil\textsuperscript{12} have been studied and this route appears promising. Some agents may not be amenable for nasal administration, for example, methadone administered by intranasal route caused a burning sensation in healthy volunteers.\textsuperscript{68}

A case report (two patients) of BTP successfully treated with intrapulmonary fentanyl administration was published.\textsuperscript{52} This route may offer a speed of onset rivaling intravenous drug administration due to rapid access to the circulation via the pulmonary capillary bed. Further studies are needed to define the role of intrapulmonary medications in the management of breakthrough pain.

**Table 14.** Direct comparison of oral transmucosal fentanyl citrate (OTFC) vs. intranasal fentanyl spray (INFS).

<table>
<thead>
<tr>
<th></th>
<th>OTFC</th>
<th>INS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to onset of ‘meaningful’ pain relief [minutes]</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>PID\textsubscript{10} [NRS]</td>
<td>1.08</td>
<td>2.27</td>
</tr>
<tr>
<td>PID\textsubscript{30} [NRS]</td>
<td>3.39</td>
<td>4.15</td>
</tr>
</tbody>
</table>

Abbreviations: PID\textsubscript{10}, pain intensity difference at 10 minutes; PID\textsubscript{30}, pain intensity difference at 30 minutes.

**Conclusion**

Recently introduced delivery systems for opioid medications represent major improvements in BTP management; however, the ideal drug or delivery system for BTP management is still unfulfilled. The time to peak analgesia of the new rapid onset opioids, such as FBT, is still longer than the time to peak pain of many BTP episodes. Thus, the ideal BTP medication is yet to be found. Studies are needed to expand our knowledge about the different patho-physiological mechanisms involved in BTP and to help us understand the variability of BTP within the individual patient. If the intensity of BTP is variable within the individual patient, the initial dose titration paradigm used to define the effective analgesic dose of BTP medication could be inappropriate, being too high for some BTP episodes and too low for others. The ideal BTP medication would provide dosing versatility to address this intra-patient variability of BTP intensity. New fentanyl delivery systems offer theoretical advantages over short acting (regular release) oral morphine and patients seem to prefer the rapid onset opioids over morphine for BTP management. Studies that directly compare a rapid onset fentanyl preparation (FBT) and oxycodone are underway in the USA. More studies that compare rapid onset opioids and standard drugs like morphine and oxycodone regular release (short acting) in diverse patient populations are needed to help us define the full benefit of matching the time course of action of the analgesic to the BTP.

**Disclosures**

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors report no conflicts of interest.

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