1. GENERAL PRINCIPLES

- Breakthrough cancer pain (BTcP) is thought to occur frequently particularly in patients with advanced disease. A pan-European survey suggested that BTcP occurs in over 60% of cancer patients prescribed analgesics.\textsuperscript{1}

- BTcP describes transient exacerbations of pain, which occur in patients with a history of well controlled background cancer pain.\textsuperscript{2,3} (see Figure 1)

- Two type of BTcP exist:-

  \textit{Incident pain}, which can be precipitated by predictable volitional factors (e.g. walking) or unpredictable non-volitional factors (e.g. coughing),

  \textit{Spontaneous pain} that occurs unexpectedly.\textsuperscript{2}

- Optimal management of BTcP requires independent assessment and targeted individualised treatment.\textsuperscript{4}

- BTcP has been traditionally been managed with opioids. However, oral short release opioids may not match the temporal characteristics of the BTcP episode.\textsuperscript{2}

- Fentanyl citrate is a lipohilic opioid that is rapidly absorbed across mucosal membranes. Some of the fentanyl products which are licensed for the management of BTcP are listed in Table 1.\textsuperscript{5-15}

- Interventional techniques (e.g. neuraxial drug infusion, neural blockade, or neuromodulation) may be indicated and should be discussed at an early stage.\textsuperscript{4}

2. GUIDELINES

- The optimal management of BTcP requires an individual approach.\textsuperscript{4} [Level 4]

- There are currently no validated assessment tools for the diagnosis of BTcP. The diagnosis of BTcP should be made according to accepted definitions in the literature.\textsuperscript{2,3} (see Figure 1). [Level 4]

- Patients with BTcP should have the pain specifically assessed to determine the aetiology, the pathophysiology and to highlight any factors that would indicate or contra-indicate specific interventions. It is helpful to use a pain assessment tool.\textsuperscript{4} [Level 4]
The underlying cause of the pain should be defined and where possible treated.\(^4\) [Level 4]

Consideration should be given to avoidance / treatment of the precipitating factors of the pain.\(^4\) [Level 4]

Consideration should be given to modification of the background analgesic regimen. Dose titration and rotation of opioids may be required \((\textit{see Guidelines on Opioid Substitution})\). Adjuvants and non-opioids should be used as appropriate.\(^4\) [Level 4]

The decision to use a specific opioid preparation should be based on a combination of the pain characteristics, the characteristics of the drug, the patients' response to opioids (in terms of efficacy and tolerability) and the patient's preferences for the individual preparation.\(^2,4\) [Level 4]

Immediate-release opioids are the rescue medication of choice in the management of episodes of breakthrough pain. Evidence would suggest that rapid-onset fentanyl products are more suitable for a typical episode of BTcP.\(^4,6\) [Level 1]

Non-opioid analgesia (e.g. paracetamol, non steroidal anti-inflammatory drugs (NSAIDs) may be useful in the management of breakthrough pain episodes.\(^4,16\) [Level 4]

Interventional techniques (e.g. surgical, anaesthetic, radiotherapy) may be indicated.\(^9\) These options should be discussed early with the appropriate specialist whilst the patient remains fit enough to tolerate any procedure \((\textit{see Guidelines on Interventional Pain Techniques})\). [Level 4]

Non-pharmacological methods such as massage, heat packs or relaxation therapy may be useful in the management of breakthrough pain episodes. Involvement of physiotherapists may be useful in the management of patients with incident pain related to movement.\(^4,17-20\) [Level 4]

### 2.1 Rapid-onset Fentanyl Citrate Preparations

Rapid-onset fentanyl citrate products should only be used in patients receiving maintenance opioid and who are taking the equivalence of at least 60 mg of oral morphine daily for a week or longer or equivalent. i.e. at least 25 micrograms of transdermal fentanyl per hour; at least 40 mg of oxycodone daily,(if using a 3:2 conversion) at least 8 mg of oral hydromorphone daily)\(^21-25\). [Level 4]

The dose of the rapid-onset fentanyl citrate products should be titrated in accordance to the product-specific dose titration guidance.\(^2\) This process should be clearly documented in the medical record or prescription charts. [Level 4]

Staff should be trained in the use of titration schedules of specific preparations. The appropriate titration charts should be used in order to ensure appropriate dosing. The dose of rapid-onset fentanyl citrate medications should be determined by individual titration.\(^3,7,13,26,27\) [Level 2]
- Patients using rapid-onset fentanyl citrate preparations may still receive alternative short-acting opioids (e.g. Oramorph®) on an as-required basis for their BTcP episodes.²

- Patients taking rapid-onset fentanyl citrate products should be regularly assessed to monitor compliance and adverse effects.² [Level 4]

- Fentanyl is metabolized by the CYP3A4 isoenzyme in the liver and intestinal mucosa. Therefore caution is required in patients taking CYP3A4 inhibitors such as macrolide antibiotics (e.g. erythromycin), azole antifungals (e.g. ketoconazole, itraconazole, and fluconazole) and certain protease inhibitors (e.g. ritonavir). These medications may increase the bioavailability of fentanyl and may also decrease its systemic clearance which may result in increased or prolonged opioid effects. Similar effects could be seen after concurrent ingestion of grapefruit juice, which is known to inhibit CYP3A4.²⁺⁻²⁵

- Patients’ opioid usage should be monitored carefully in the community with particular attention to their maintenance therapy and potential accidental exposure.² Patients with uncontrolled breakthrough pain (i.e. more than 4 episodes of pain in 24 hours) should have at least weekly follow up as an outpatient, and 48 hourly reassessment if an inpatient. [Level 4]
### Table 1 Rapid-onset Fentanyl citrate products which are available for the use in the management of breakthrough cancer pain\(^{21,22,24,25}\) [Level 1]

<table>
<thead>
<tr>
<th>Name of drug</th>
<th>Route/ Formulation</th>
<th>As required Fentanyl Doses available</th>
<th>Additional Notes</th>
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<tbody>
<tr>
<td>Actiq(^{®})</td>
<td>Oral transmucosal Lozenge</td>
<td>200,400, 600,800, 1200,1600 microgram</td>
<td>Application site reactions, including gum bleeding, irritation, pain and ulcer have been reported. (^{21})</td>
</tr>
<tr>
<td>Effentora(^{®})</td>
<td>Buccal Tablet</td>
<td>100, 200, 400, 600, 800 microgram</td>
<td>Application site reactions including bleeding, pain, ulcer, irritation, paraesthesia, anaesthesia, erythema, oedema, swelling and vesicles.</td>
</tr>
<tr>
<td>Abstral(^{®})</td>
<td>Sublingual Tablet</td>
<td>100, 200, 400, 600, 800 microgram</td>
<td></td>
</tr>
<tr>
<td>Instanyl(^{®})</td>
<td>Intranasal Spray</td>
<td>50, 100, 200microgram</td>
<td>Contraindicated if previous facial radiotherapy or recurrent episodes of epistaxis. Concomitant use of nasally administered oxymetazoline has been shown to decrease the absorption. It is recommended that concomitant use of nasal decongestants is avoided. Application site reactions such as epistaxis, nasal ulcer, rhinorrhea have been reported. If intranasal products have not been used for more than 7 days the pump must be sprayed once in the air before the next dose is taken.</td>
</tr>
<tr>
<td>PecFent(^{®})</td>
<td>Intranasal Spray</td>
<td>100, 400 microgram</td>
<td>Concomitant use of nasally administered oxymetazoline has been shown to decrease the absorption. It is recommended that concomitant use of nasal decongestants is avoided. Application site reactions such as epistaxis, nasal ulcer, rhinorrhea have been reported. If intranasal products have not been used for more than 7 days the pump must be sprayed once in the air before the next dose is taken.</td>
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Figure 1  Simple algorithm for the assessment of breakthrough cancer pain (adapted with permission from the author²)

Does the patient have background pain?
(Background pain = pain present > 12 hours/day during previous week (or would be present if not taking analgesia))

YES

Is the background pain adequately controlled?
(Adequately controlled = pain rates as "none" or "mild", but not "moderate" or "severe" for > 12 hours/day during previous week)

YES

Does the patient have transient exacerbations of pain?

YES

Patient has breakthrough pain

NO

NO

Patient does NOT have breakthrough cancer pain

YES

Incident pain

NO

Spontaneous pain
3. **STANDARDS**

1. All patients with cancer should be assessed for the presence of breakthrough pain. [Grade D]

2. The aetiology of the breakthrough pain should be identified in all patients. [Grade D]

3. A pain assessment tool (e.g. numeric pain score, pain diary) should be used to assess pain and the response to interventions in all patients with breakthrough cancer pain. [Grade D]

4. When initiating rapid-onset fentanyl citrate products, all patients should have their dose titrated using the product-specific manufacturers' titration schedule, until their individual standard breakthrough dose is set. This process should be recorded clearly in the medical record or prescription chart. [Grade B]

5. Patients with uncontrolled breakthrough pain (i.e. more than 4 episodes of pain in 24 hours) should have at least weekly follow up as an outpatient, and 48 hourly reassessment if an inpatient. [Grade D]

4. **REFERENCES**


8. Coluzzi PH, Schwartzberg L, Conroy JD, Charapata S, Gay M, Busch MA et al. Breakthrough cancer pain: a randomized trial comparing oral transmucosal...


5. GUIDELINE DEVELOPMENT GROUP

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