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Management of Breakthrough Pain in Patients with Cancer

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Abstract

Breakthrough pain (BTP) in patients with cancer lacks a consensus definition and is subsequently inadequately diagnosed and assessed, therefore making it more challenging to manage. Cancer pain is generally moderate to severe in intensity and persistent in nature. Despite the problematic definition of BTP, it is generally described as having similar intensity, but may also be transitory and variable in predictability. Most breakthrough analgesia fails to be effective in the time required for BTP. No useful analgesia is therefore provided but drug adverse effects escalate. Cancer pain management relies on the WHO analgesic ladder. The frequency of BTP and its inadequate management means that it has significant adverse effects on patients, their families and those involved in their care. This article outlines a systematic, clinical and evidence-based approach to managing BTP in patients with cancer that emphasizes a holistic approach and an understanding of multidimensional 'total pain'. Guidelines for managing BTP are presented and areas of developing research are identified.

1. Breakthrough Pain (BTP)

A total of 50–70% of patients with cancer receiving active treatment are estimated to have pain.[1-5] At diagnosis, the prevalence is suggested to be 30–40% [3,6-8] and rises to 70–80% in those with advanced disease.[9-12] These figures would justify the fear cancer patients articulate about experiencing pain. Much has been achieved in controlling cancer pain but the area of breakthrough pain (BTP) has remained problematic.

A lack of awareness coupled with inadequate assessment and appropriate treatment for BTP in patients with cancer leads to sub-optimal management and distress for all concerned. BTP has been shown to affect both patient and carers' quality of life (QOL) through dissatisfaction with treatment, functional debility, and increased anxiety and depression.[13] BTP is recognized as a poor prognostic indicator,[14,15] and its management has been demonstrated to burden the healthcare system in terms of hospital visits, QOL and admissions.[16,17]

1.1 Definition

BTP has been considered as the pain that 'breaks through' the analgesia controlling the more stable pain pattern (baseline pain). An agreement upon a unifying definition remains elusive.[15,18-21] The semantics continue to revolve around the nature of the baseline pain.

For the purpose of this article, BTP will be defined by a broader definition used by Svendsen et al.,[22] rather than that proposed by Portenoy and Hagen.[18] This includes uncontrolled baseline pain and therefore incorporates pain experienced during titration of analgesic therapy. Svendsen et al.[22] define BTP as "episodic flares of pain on a treated or untreated baseline pain". Using our definition of BTP, it may be divided into three subtypes (end-of dose failure, incident pain, and idiopathic or spontaneous pain).

1.1.1 End-of-Dose Failure

This is experienced by patients with uncontrolled baseline pain. In this situation, there is inadequate treatment from the baseline analgesia and further titration to establish control is required. This subtype occurs in 17–30% of patients.[18,23]

1.1.2 Incident Pain

Here, BTP occurs upon a baseline of controlled pain, as a result of a precipitating event. It occurs in 50–60% of patients with BTP,[18,24] and should promote a review of the type and cause of the pain. Other treatment modalities may subsequently emerge to treat the cause or provide adjuvant therapies. Incident pain may be further divided into the following two categories:

- Predictable incident pain – in this case, the stimulus can be anticipated and therefore medication can be used to pre-empt the onset of pain. Examples include movement (e.g. walking, standing), coughing, swallowing and touch.
- Unpredictable incident pain – the causes of pain in this instance are more involuntary or visceral in nature (e.g. colic or ischaemic).

1.1.3 Idiopathic or Spontaneous Pain

In this instance, baseline pain is once again controlled but no precipitating cause is present, for example in neuropathic pain. This subtype occurs in 20–60% of patients with BTP.[18,21,23,24]

1.2 Prevalence

A meta-analysis of studies suggested a prevalence of BTP of 24–95%[22] based on various definitions used in studies between 1988 and 2004. Although this was narrowed to 65% by an international survey of pain specialists across 24 countries, a consensus definition was notably lacking.[25] However, there is an almost identical prevalence figure of 64% from the pioneering work of Portenoy and Hagen.[18]

Therefore, in almost 2 decades, there has been very little change in the prevalence of BTP despite the improvements in controlling baseline pain.[18,26,27] The experience from palliative management coupled with the recent treatment advances and resurgence of interest in BTP may improve this situation.

1.3 Characteristics

BTP is usually moderate to severe in intensity, in keeping with cancer pain.[25] It reaches a maximal intensity within 3–5 minutes and lasts an average of 15–30 minutes. Episodes occur with a mean frequency of four to seven times per day.[13,18,23,28]

The subtype of end-of-dose failure is characteristically typical of cancer pain. It does not display the same temporal profile of quick onset and duration as the other subtypes. Subsequently, its inclusion as a subtype of BTP has caused confusion. This difference in the nature of the pain has been a major problem in addressing BTP appropriately.[15,22]

1.4 Assessment

Saunders[29] introduced the concept of 'total pain'. Each death emphasized that it was as unique as the life that preceded it. This described the psychological, social, spiritual and physical influences on the pain experienced by the patient and family, and has since become integral to the palliative holistic approach.[30]

The assessment of 'total pain' provides a view of the patient with the disease, rather than the disease of the patient. Psychosocial and existential issues may be more important to the patient than their physical symptoms. A dialogue that facilitates the patient telling their story and identifying their concerns should be encouraged; this also provides an opportunity for patient education and counselling. This approach may reveal, for example, drug noncompliance through personal health beliefs, poor coping mechanisms in the adaptation to disease progression and/or anticipation of pain from a fear of cancer. Such findings can be addressed to improve management outcomes.

The main medical aim of assessment is the identification of the site, severity, type, nature, duration and cause of the BTP. A specific assessment tool has been developed by Zeppetella and Ribeiro,[31] but is not widely used. An adaptation of this assessment tool for BTP in cancer patients has recently been validated nationally and internationally. This should promote a standardization of the approach to BTP within a clinical setting, as well as a consensus definition and much needed education.[32]

2. BTP Management

A management algorithm for BTP has been proposed in figure 1.[22,33] This section provides further information about the options of management available.

2.1 Non-Pharmacological Approaches

Better assessments can inform pharmacological and adjuvant treatments, but there are usually non-pharmacological options that may improve both baseline pain and BTP. These are listed in table I.

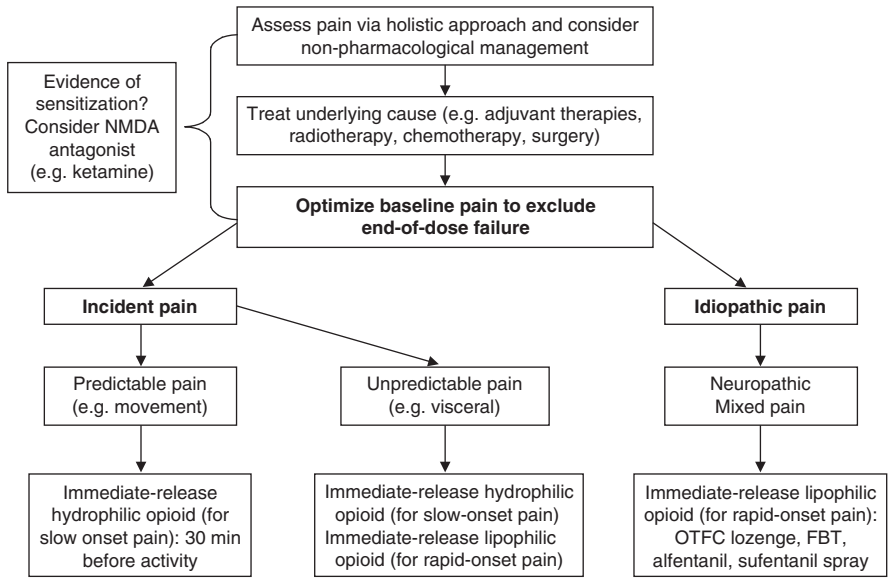

Fig. 1. Algorithm for the management of breakthrough pain in patients with cancer. **FBT** = fentanyl buccal tablet; **NMDA** = N-methyl-D-aspartate; **OTFC** = oral transmucosal fentanyl citrate.

Table I. Non-pharmacological approaches to pain management[34,35]

Physical	Changing position Massage Hot/cold compress Acupuncture ± opioids[34] TENS – uncertain evidence for analgesic effect[36] Exercise – stretching, warming up, maintaining good posture[33] Orthotic aids to stabilize painful pathological fracture sites
Behavioural	New sequencing of events to perform a task Pacing of activities to cope with pain/fatigue Re-framing of expectations
Psychological	Visualization Guided imagery Hypnosis Counselling Music therapy

TENS = transcutanous electrical nerve stimulation.

2.2 Pharmacological Approaches

In 1997, Portenoy[37] proposed a three-step management strategy for BTP, which is still valid today. In conjunction with the WHO analgesic ladder, this involves the following: (i) consideration of adjuvant therapies to treat the underlying cause; (ii) optimization of baseline analgesia; and (iii) use of specific analgesics to match the temporal nature of the pain.

Cancer pain is usually treated with simple analgesics and opioids, as guided by the WHO analgesic ladder and the philosophy of giving medication to provide analgesic cover at all times (i.e. around-the-clock analgesia). This approach controls pain in up to 88% of patients with cancer.[38,39] It is important to note that certain types of pain, for example, bone pain or neuropathic pain, are only partially responsive to opioids. Hence, adjuvant therapies targeting these pain syndromes may slow the rate of opioid dose escalation and, thus, avert opioid adverse effects (e.g. nausea, vomiting, drowsiness, myoclonus, confusion and constipation).

2.2.1 Adjuvant Therapies

Adjuvant therapies should target the underlying pathology of the pain. Cancer pain can be classified as somatic, visceral or neuropathic in type, as a result of tumour invasion or iatrogenic causes. Often, a mixed picture is seen with regard to both type and cause. BTP is not dissimilar and predominately emanates from the same area as the baseline pain.[18,28] Therefore, adjuvant therapies provide a benefit to both baseline pain and BTP in conjunction with opioids.[28] More interventional approaches are also useful, but careful selection of those who may benefit and when they should be referred is essential. Table II lists the relevant adjuvant therapies for BTP. Notable omissions, as a result of recent evidence, include calcitonin[40] and cyclo-oxygenase 2 inhibitors (benefit outweighed by cardiovascular and oncogenic risks, as well as adverse effect profile).[41] Much of the evidence for the use of antineuropathic agents is based on non-malignant disease, for example, diabetic neuropathy and trigeminal neuralgia.

2.2.2 Optimization of Baseline Pain

The second step in Portenoy's BTP management strategy ensures the exclusion of end-of-dose opioid failure. Ensuring that baseline pain is well managed is part of basic cancer pain management. An indication of the potential for further optimization of treatment is the efficacy of the immediate-release opioid. If this is still effective for flares of pain then optimization of baseline pain is feasible. A lack of efficacy should prompt a review, as adjuvant therapies may be necessary. The importance of this is demonstrated by the ineffective opioid escalation for pain that heralds spinal cord compression.[69,70]

Immediate-release preparations of opioids, such as morphine, hydromorphone and oxycodone, are effective in this subtype of BTP. The doses of immediate-release preparations used guides titration of the slow-release counterpart, so that generally the same drug is used in two different preparations.[71,72]

The rescue dose (dose used to treat the BTP) of the immediate-release preparation is generally calculated as one-sixth of the total daily opioid dose,[71] although evidence for this is minimal (the rationale being that each immediate-release rescue dose should last 4 hours and so equates to 6 doses in 24 hours if needed). For example, a dose of slow-release morphine 30 mg twice daily would require a rescue dose of immediate-release morphine 10 mg every 4 hours as required. Despite this being part of basic cancer pain management, up to 40% of patients with BTP have been found to have no prescribed rescue dose.[23]

Table II. Adjuvant therapies in pain management

Type of pain	Adjuvant therapy
Bone pain	NSAIDs[42,43] Corticosteroids[44,45] Bisphosphonates[46,47] – pamidronate,[48] zolendronic acid,[49] ibandronate[50] Radiotherapy[51] Radionuclides – Strontium-89,[52] Samarium-153[53] Vertebroplasty[54,55]
Neuropathic pain	Corticosteroids[56] Tricyclic antidepressants[57] – amitriptyline, nortriptyline, desipramine, imipramine Anticonvulsants – gabapentin,[58,59] pregabalin,[58] (topiramate, valproate, lamotrigine)[58] Benzodiazepines – clonazepam[60] Other antidepressants[58] – paroxetine, venlafaxine NMDA antagonists – ketamine,[61,62] methadone[58] KOD (ketamine, opioid, dexamethasone)[63] Cannabinoids[58,64] Topical agents – capsaicin, lidocaine patch[58] Nerve blocks, nerve decompression, chordotomy
Visceral pain[65,66]	Anticholinergics – hyoscine butylbromide, hyoscine hydrobromide, glycopyrrolate Somatastatin analogue – octreotide Corticosteroids
Muscle spasm	Muscle relaxants – benzodiazepine, baclofen
Intractable pain	Spinal analgesia[67,68] – local anaesthetic, opioid and clonidine
Tumour-related pain	Surgery Chemotherapy Radiotherapy

NMDA = N-methyl-D-aspartate.

Cautious titration of immediate-release opioids allows monitoring for adverse effects as well as efficacy. Frequent rescue doses may warrant an increase in baseline analgesia as well as a clinical review. The slow-release dose should be increased if the total immediate-release dose is proportionally at least 33% of the slow-release dose over 24 hours. Hence, for our example here, the slow-release morphine dose of 30 mg twice daily would only be increased if the total 'rescue doses' were greater than 20 mg over 24 hours. If it was clinically indicated in this case, the new slow-release morphine dose would be (30 + 30 + 20)/2 = 40 mg twice daily.

There should also be an increase in the immediate-release dose, calculated as one-sixth of the total opioid dose in 24 hours (immediate and slow release). This would be 80/6 = approximately 13 mg or for easy prescribing 10–15 mg every 4 hours as required. Baseline pain should not require more than two rescue doses per 24 hours when it is controlled. Two-thirds of patients never require more than 180–200 mg of morphine per 24 hours. The remainder may need up to 1200 mg over 24 hours to gain adequate analgesia.[73]

Optimization of the opioid dose may also involve a change in drug delivery (e.g. poor opioid absorption) or a switch from one opioid to another (e.g. due to adverse effects or opioid-induced tolerance).[74] A reduction in the administration interval is occasionally warranted in order to maintain analgesic efficacy.[33] For example, a slow-release preparation of morphine may be prescribed every 8 hours rather than the usual every 12 hours. Morphine remains the opioid of choice for cancer pain, probably because of its variable routes of administration, the experience gained over time (and therefore familiarity of effects and adverse effects) and the absence of a better, freely available potent opioid.[41]

Methadone is an opioid with N-methyl-D-aspartate (NMDA) antagonist effects and is a readily available neuropathic agent that spares renal function. It is sometimes used instead of morphine when these factors are prominent, but repeated doses can cause drug accumulation leading to toxicity. Unpredictable pharmacokinetics hinders the use of methadone to those who have considerable experience in prescribing it.[75,76]

Table III compares the pharmacokinetics of some oral immediate-release opioids.[73] The subtype of end-of-dose failure requires the use of these preparations to gain control of baseline analgesia. The other BTP subtypes usually require faster acting agents with shorter half-lives.

Table III. Comparison of oral immediate release opioids

Drug	Onset of action (min)	Duration of action (h)
Morphine	30–40	3–6
Hydromorphone	30	4–5
Oxycodone	30	4–6
Methadone	10–15	4–6 (6–12 when repeated)

2.2.3 Specific BTP Analgesia

BTP medication should be of appropriate rapidity of onset, potency and administration to control BTP. In end-of-dose failure, the same opioid is recommended to be used for both BTP and baseline pain.[71,72] In specific BTP, this is not necessarily possible because of the different temporal requirements of the opioid analgesics in response to the pain.

Immediate-release morphine is usually effective 30–40 minutes after oral administration. Therefore, it is not usually effective for unpredictable incident or idiopathic BTP, but could be used in predictable incident BTP (see figure 1). Doses taken at least 30 minutes before the exacerbating activity can provide good pain relief.[35] The adverse effects of morphine from frequent administration can be a clinical restriction and behavioural adaptations may limit repeated use.

Drugs have been used via different routes to increase their absorption and efficacy in BTP. Fast pain relief may be provided by intravenous methadone (2–5 minutes to effect) or morphine (15–30 minutes to effect). Intravenous patient controlled analgesia (PCA) devices limit toxicity, providing quick pain relief as needed.[72] Intravenous morphine has also been used for BTP at 20% of the total daily oral morphine dose.[77] However, these modalities are predominantly dependent on the availability of intravenous access and the possible complications of toxicity even with PCA devices.[78] This poses a problem, particularly in a community setting. Similarly, intrathecal interventions with morphine and local anaesthetics are helpful in incident pain,[79] but should not be considered if community support is lacking. More research is needed to elucidate the role of intrathecal analgesia in BTP.

Oral (buccal and sublingual) and intranasal routes have subsequently emerged as the best options for BTP medications, mainly because of rapid absorption from a highly vascular area, which avoids first-pass metabolism and enhances simple administration. The nasal administration of opioids has been recognized as an effective management option and a potential PCA to rival the intravenous route.[80] Intranasal morphine has been used for BTP,[81] but there has been a recognition of the further benefit with lipophilic opioids.[79] These opioids (e.g. fentanyl, alfentanil, sufentanil and methadone) are more readily absorbed from the nasal and oral mucosae, unlike hydrophilic opioids (e.g. morphine). Methadone has been noted to have a rapid onset of analgesia[82] but its complex pharmacokinetics limit its use in BTP. Successful options include fentanyl derivatives and NMDA antagonists.

Fentanyl

Fentanyl is a selective synthetic opioid agonist, acting on the μ-opioid receptor. It has been commonly used for chronic cancer pain in the form of a transdermal patch, but other preparations have been trialled in anaesthetics, for example, via nebulizer and intranasal spray.[83,84] Fentanyl is approximately 80-fold more potent than morphine[85] and its pharmacokinetic profile has suited the required characteristics of a BTP analgesic more than morphine. The transmucosal route has been comparable with parenteral fentanyl, partly due to its lipophilic properties and the absorption factors mentioned here. It has a rapid onset of action (5–10 minutes), short duration of action (30–60 minutes) and inactive metabolites.[86-88] Subsequently, fentanyl formulations and analogues have been used to treat BTP.

Fentanyl Analogues: alfentanil has a faster onset (2–5 minutes) and a shorter duration of action (10–15 minutes) than fentanyl. It is also a selective μ-opioid receptor agonist, with a plasma half-life of 100 minutes and a potency that is one-quarter that of fentanyl.[73] The potential use of intranasal alfentanil was recognized in 1995.[89] Positive preliminary results observed for intranasal fentanyl[83,90,91] led subsequent investigators to examine the efficacy of intranasal alfentanil for BTP. The maximum volume that can be delivered in a single administration to one nostril in humans is 0.15 mL.[80] Larger volumes lead to pharyngeal deposition and subsequent gut absorption, which would reduce opioid efficacy from the nasal delivery and via first-pass metabolism. Different nasal sprays exist and various additives can enhance the efficacy from such small volumes. Duncan[92] describes using a spray that delivered 7 μg of fentanyl per spray. However, alfentanil could be delivered at 70 μg per spray, using the same device, because of its more soluble

properties. Intranasally, alfentanil provides a bioavailability of 64.96%.[89] This has favoured its use as an intranasal spray for incident pain and has been a clinically effective option in a palliative setting.[92]

Sufentanil was used intranasally in a comparative study with intravenous sufentanil in post-operative patients. This demonstrated the intranasal route as a rapid and effective alternative to the intravenous route.[93] Sufentanil is 10-fold more potent than fentanyl, and has a bioavailability of 70% intranasally and 50% sublingually.[93,94] The intranasal route offers greater predictability of drug absorption as some is swallowed when administered sublingually. The pharmacokinetic profile of sufentanil is more like fentanyl than alfentanil, and studies would suggest that it is well tolerated and effective for the management of BTP.[95]

Oral Transmucosal Fentanyl Citrate: the oral transmucosal fentanyl citrate (OTFC) lozenge was developed for the management of BTP. Clinically, it has been validated against placebo[86] and morphine.[96] A Cochrane review has demonstrated it to be an effective management option for BTP.[97] It is indicated for relief of BTP with concomitant regular strong opioid therapy (morphine >60 mg/day).

The onset of analgesia using the OTFC lozenge occurs at 5–10 minutes and lasts for 1–3.5 hours with a plasma half-life of 6 hours. The bioavailability is 50% in total (25% absorbed from the buccal mucosa and the other 25% via the gastrointestinal tract).[73]

The starting dose is a 200 μg lozenge, irrespective of the regular opioid dose. A lozenge is consumed over 15 minutes by rubbing it on the inside of a cheek and alternating cheeks periodically. If after 15 minutes no adequate pain relief has been obtained, another 200 μg lozenge may be consumed. No more than two lozenges should be used per episode of pain. After three episodes of pain, if this use of the 200 μg lozenges remains ineffective, then the dose should be increased to a 400 μg lozenge. This should be used in the same way to titrate the dose to control the BTP. Lozenge strengths increase as follows: 600, 800, 1200 and 1600 μg. Approximately 25% of people gain no benefit from the 1600 μg lozenge or experience adverse effects that prevent its use. Once the dose has been titrated, no more than four doses should be used per day. The regular opioid could be increased if more doses are needed, which may require a re-titration of the OFTC.[73]

Zeppetella and Ribeiro[97] have recently used the OTFC to confirm that BTP medication with a controlled baseline pain should be used differently from the way it is used in end-of-dose failure (i.e. the therapeutic BTP dose is not a proportion of the controlling baseline pain dose). The review concluded that rescue doses could be titrated as tolerated, on an as needed basis, to achieve clinical efficacy.

Although the OTFC does provide pain relief for BTP in patients with cancer, it does have some limitations. The time taken to reach therapeutic concentrations has been regarded as too long, the citrate matrix has been associated with dental problems and debilitated patients display limited compliance with use.[98]

Fentanyl Buccal Tablet: the fentanyl sublingual tablet that preceded the fentanyl buccal tablet (FBT) dissolved rapidly. It produced detectable plasma drug concentrations within 8–11 minutes and proved the sublingual absorption to be more reliable than the OTFC.[99]

As with the OTFC, the FBT provides analgesia in clinical scenarios of opioid tolerance. The tablets are placed between the gum and the cheek for absorption (tablet strengths are 100, 200, 400, 600 and 800 μg). A novel effervescent delivery system increases the absorption of the FBT. This property may imply better pharmacokinetics compared with the sublingual tablet, but no studies have confirmed this. However, the effervescent system does facilitate maximum serum concentrations, which are detected earlier and at higher levels than with OTFC. Dose titration should commence at 100 μg and analgesic onset anticipated after a minimum of 15 minutes. One further dose can be used after 30 minutes for the same episode of pain.[98]

However, the elimination of the FBT shows a slower phase at doses above 800 μg, allowing greater bioavailability and producing a longer half-life.[100] Individual variations in drug elimination may also be of concern as the half-life ranges between 1 and 5 hours for some individuals, and 14 and 32 hours in others over a single dose range of 100–800 μg.[101,102] It is important to note that these results are from healthy volunteers rather than can-

cer patients with deteriorating drug clearance mechanisms.

Doses between 100 and 800 μg are well tolerated overall, although oral mucosal ulcers have been noted at the site of application. Assessments of pain intensity made at 15-minute intervals after use show clinical improvement over a 1-hour period as well as a reduction in extra medications used.[103]

N-Methyl-D-Aspartate Antagonists

It is suggested that peripheral and/or central sensitization may be associated with BTP. The clinical expressions of sensitization (allodynia and hyperalgesia) may reflect a lower threshold in peripheral nerve excitation or enhanced responsiveness to pain transmission in the CNS (central sensitization). Activated NMDA receptors are also known to be involved in this process, but more research is needed and may highlight a role for NMDA antagonists.[22]

BTP is often associated with neuropathic, bone or mixed pain, where the clinical states of tolerance and wind-up have occurred. Dextromethorphan and methadone have been used as weak NMDA antagonists as they have less adverse effects than the stronger NMDA antagonist ketamine. Dextromethorphan has not shown any benefit in recent trials with regards to resolving or improving these clinical states,[104] but whether the timing of its use in conjunction with opioid analgesia is important remains to be seen. Sublingual methadone has been used in a recent pilot study for BTP and displayed pain relief with a median onset of 5 minutes. Doses ranged between 2 and 18 mg, and toxicity was mild or similar to previous BTP analgesia. Further research is required with awareness of the unpredictable pharmacokinetics of methadone.[105]

Ketamine is a commonly used anaesthetic agent, but in subanaesthetic doses it can be used as an adjuvant therapy for cancer pain. It is especially used when opioid monotherapy has proven ineffective, and has been used as 'burst therapy'[62] and triple therapy.[63] Intranasal use has been shown to provide rapid, well tolerated and effective relief, specifically for BTP, but requires further research.[106] Ketamine is known to have psychotomimetic adverse effects, which are dose related,[62] but use of a benzodiazepines or haloperidol may prevent or manage these effects.[107,108] The use of ketamine in BTP seems to be a logical consideration as a possible treatment option to affect the involvement of NMDA in the clinical picture.

3. Clinical Considerations

The efforts to optimize opioid analgesia continue to be reviewed and overlap with aspects of BTP management. Hanks et al.[79] and Walsh[109] highlight the fact that 20–40% of patients taking morphine have dose-limiting adverse effects and subsequently poorly controlled pain. Lipophilic opioids for rapid-onset BTP are metabolized more quickly than opioids used for baseline pain, thereby limiting the adverse effect profile of the total opioid intake. Nausea and vomiting have been recognized as a limitation in opioid therapy and occur in approximately 25% of patients.[110,111] The usual options for patients with such adverse effects are as follows: (i) to reduce the opioid dose (which may be assisted by the use of adjuvant analgesics); (ii) to use symptomatic management; (iii) to employ opioid switching; or (iv) to change the route of opioid delivery.[79,109,112,113]

The rapidity of onset of BTP determines the immediate-release opioid of choice. Slow onset BTP (e.g. predictable incident pain) would best be treated with a hydrophilic opioid. Idiopathic pain has a rapid onset and, hence, a lipophilic opioid would be useful. It is useful to note that the doses of the lipophilic agents for BTP are not likely to have any proportional relationship with the baseline analgesic dose. For unpredictable incident pain, a strategy that uses analgesia according to the temporal nature of the BTP may provide the best course of management (see figure 1).

Opioid switching involves the cessation of an opioid that has become less efficacious, or problematic with regard to adverse effects, and the commencement of a new opioid. The concept of phasing out one opioid and introducing a new one (to the extent that the former is not stopped [i.e. partial opioid switching]) has also been raised.[114-116] The aim is to improve analgesia with less toxicity and dose escalation, which are also the reasons for opioid rotation. Further research is being driven by the clinical concepts of opioid switching, sensitization and the development of tolerance. The interplay at the opioid receptor is being recognized as a more

intricate process than was previously assumed and investigations of this interplay may lead to the production of more effective synthetic opioids.

Although partial opioid switches have been hailed as an advance in opioid therapeutics,[117] such combinations should be regarded as experimental. There is currently no evidence from randomized clinical trials to guide opioid combinations of this kind.[41]

4. Future Developments

In terms of specific BTP advances in treatment, a 'pain pen' has been trialled using hydromorphone, morphine or sufentanil for subcutaneous rescue dose administration.[118] Recently, the very old analgesic modality of inhaled nitrous oxide has been applied to treat incident pain in a blinded case series.[119] Both the pain pen and inhaled nitrous oxide have been considered for BTP treatment that is difficult to manage. Morphine has now been developed as an effervescent preparation and a recent study favourably compared it against immediate-release morphine.[120] Pain scores were lower, pain relief was significantly quicker (13 ± 5.6 minutes compared with 27 ± 4.4) and two-thirds of the participants felt it was better than the immediate-release preparation. This may herald a means of limiting toxicity and providing a simpler regimen for the management of BTP. The FBT and intranasal ketamine look promising and have also been shown to be useful in non-malignant pain.[106,121] More research with ketamine and the various fentanyl derivatives may be able to further characterize their pharmacodynamics and pharmacokinetics. Such characterization may permit tailoring the analgesic regimen of each patient to the temporal nature of the BTP experienced. The future management of BTP appears to be promising not only in terms of pharmacological advances, but also with regard to our increased awareness of the problem.

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