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REVIEW

Current and Emerging Pharmacotherapies of Breakthrough Pain in Cancer

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Abstract: Breakthrough pain (BTP), defined as "transitory episodes of sudden severe pain that occur on a background of otherwise controlled pain" is common and disturbing for cancer patients. Optimal management of sudden, severe, and transitory episodes of BTP requires analgesics with rapid onset and short duration of effect, ideally in convenient and easily administered formulations. BTP has traditionally been treated with immediate-release oral opioids, but these analgesics are too slow in onset and have prolonged duration of effect. Recently developed and emerging pharmacotherapies exploit the properties of transmucosal absorption of lipophilic opioids in transbuccal, sublingual, and intranasal delivery systems to provide rapid and effective relief of BTP in reliable, convenient, and acceptable preparations.

Keywords: breakthrough pain, cancer pain, pain management, opioids

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Introduction

Nearly all patients with cancer experience pain at some point during their illness. Pain is estimated to occur in 30%–70% of patients early in the course of disease and typically to become more common and severe as the disease progresses.[1,2] Although most cancer pain responds well to the step-wise increase in analgesia therapy outlined by the World Health Organization,[3] a wide range (24%–95%) of cancer patients experience transitory episodes of sudden severe pain that can occur 2–7 times a day on a background of otherwise reasonably controlled pain.[1,2,4–7] These episodes are associated with decreased physical functioning, increased psychological distress, and reduced quality of life.[2,5,7–11] Such episodes are commonly referred to as "breakthrough pain" (BTP), although the definition of BTP varies widely among clinicians in different countries and specialties.[2,4,10] Although the concept of BTP has been extended to patients with non-malignant chronic pain, serious concerns have been expressed about the lack of efficacy and the potential for abuse when extrapolating treatment recommendations for cancer BTP to non-cancer pain.[12] Consequently, this review will be restricted to the current and emerging treatments for BTP in cancer patients.

Types of BTP

BTP has frequently been categorized as incident, spontaneous (idiopathic), or "end-of-dose" pain, and by whether pain is predictable or unpredictable.[2,10,13] End-of-dose failure, in which the patient's background pain increases prior to the next dose of analgesic, is a predictable consequence of under dosing of or of escalating tolerance to opioids. Of note, because the underlying background pain is not controlled in these situations, many authors argue that end-of-dose failure should not be included as a type of BTP.[2,7,10] The management of end-of-dose failure pain is also different from other types of BTP, as this pain can usually be successfully treated by use of scheduled rather than as needed dosing of analgesia, use of sustained-release formulations, and better understanding the pharmacokinetics of the analgesics used.

Incident BTP, occurring in an estimated 32%–94% of patients, is caused by predictable volitional movement (such as weight-bearing or change in position) or nursing cares (such as dressing changes), and by less predictable nonvolitional events (such as coughing or bowel movements). Predictable incident pain can be treated with anticipatory dosing of analgesics, whereas management of nonvolitional incident pain can be more challenging. Finally, many patients report spontaneous BTP (approximately 28%–45% of patients), which as unpredictable transitory flares of pain require different pharmacokinetic considerations than do incident or end-of-dose BTP.[1,2,7,13]

Assessment of BTP

Distinguishing between these types of BTP requires a careful history exploring factors of frequency, predictability, rapidity, duration, accompanying events, and response to current medications.[10,13] Of note, the source of BTP is often the same as the background pain, whether nociceptive, neuropathic, or some mixture of the two.[1,7] The available pain instruments routinely used to complement the standard approach to cancer pain history often fail to capture the salient clinical features of BTP.[14] Specific assessment tools for BTP have been developed—the Alberta BTP Assessment (available for download as http://www.cancerpainnet.ca/files/ABPAT%20FEB%2026%202008.pdf) has been developed as a research tool and recently validated—but these are not widely used clinically.[15,16] Physical examination may help to reveal the cause of some types of BTP, especially when provocative maneuvers are used,[17] but these are less helpful in diagnosing causes of spontaneous BTP, as well as causes of some types of neuropathic pain.

Pharmacologic Management of BTP

The data regarding the appropriate pharmacologic management of BTP in cancer patients are confounded by the use of varying definitions for both BTP and pain relief, and the study of small numbers of patients in a variety of settings with different underlying malignancies and baseline treatments.[6] Recent task force recommendations have attempted to present an organized approach to management of BTP.[4,10] Initial steps should include treatment of the underlying cancer, which is often the cause of the BTP.[4,10] Optimization of the background analgesia regimen following the WHO guidelines using scheduled opioids and adjuvant therapies may reduce the incidence of some types of

BTP.[2,6,7,10] In addition, volitional incident pain may be reduced by minimizing the stress from the precipitating factors and providing analgesia in anticipation of the activity.[6,10]

Nevertheless, traditional approaches to managing background cancer pain are often unsuccessful in many types of unpredictable BTP when of sudden onset, intense severity and brief duration. Incident and spontaneous BTP have been reported to peak rapidly with a median time of 3–5 minutes from onset to maximal pain.[1,2,7] In addition, episodes of BTP typically have a brief duration averaging about 30 minutes, with 90% lasting less than one hour.[1,2,7,18] Consequently, optimal treatment of these episodes requires delivery of analgesic therapy with comparable rapid onset and brief duration of action, ideally in a form that is easily administered and convenient for use in community settings.

Conventional approaches for treating BTP have included recommendations for as needed immediate-release oral opioids in doses ranging from 5%–20% of the total daily dose.[10,13,19,20] However, studies indicate little correlation between the effective dose of opioids for relief of BTP and that for daily background pain. For example, in a study of 188 cancer patients, the opioid dose effective for BTP was between 10%–20% of the total daily opioid dose only one-third of the time, and either more or less than this dose the remainder of the time.[21] In fact, the effective opioid dose for BTP ranged from 1% to 71% of the total daily opioid dose.[21] More importantly, the pharmacokinetics of oral opioid therapy seem poorly suited for treatment of BTP in cancer patients.[10] In one study, oral therapy with immediate-release opioids required more than 30 minutes to produce meaningful pain relief, whereas most episodes of BTP lasted only 35 minutes.[18] In addition, the accumulation of opioid due to its prolonged duration of effect (3–6 hours) can produce side effects that ultimately reduce the quality of life for patients and their families when these agents are used frequently throughout the day for BTP.[22] Consequently, although oral therapy with hydrophilic opioids (such as morphine, hydromorphone, oxycodone) can be effective for predictable types of BTP such as incident or end-of-dose failure pain, alternative agents with more favorable pharmacokinetics and use of alternative delivery routes should be considered to treat unpredictable and spontaneous types of BTP.[23]

Among the opioids, fentanyl and related compounds including sufentanil and alfentanil have favorable pharmacokinetic profiles for treatment of BTP. These potent synthetic lipophilic opioids have selective activity for μ-receptors expressed in the brain, spinal cord and other tissues. The fentanyl series of medications have low molecular weight and high lipid solubility, allowing for rapid and effective transmucosal absorption and rapid transport across the blood-brain barrier. Compared with hydrophilic opioids, they also have higher potency, better therapeutic index, and absence of pharmacologically active metabolites. Consequently, fentanyl has more rapid onset (5–10 minutes) and shorter duration of effect (30–60 minutes) compared with morphine. The newest analogue alfentanil has even faster onset (2–5 minutes) and shorter duration of activity (10–15 minutes). Until recently, these medications were only available in parenteral formulations, but newer transmucosal delivery systems have been developed (discussed below).

Non-oral delivery routes for opioids include parenteral administration (intravenous [IV], intramuscular [IM], and subcutaneous [SC]) which produces a more rapid onset of effect that is better suited to treatment of unpredictable BTP. Many opioids, including morphine, fentanyl, hydromorphone, and oxycodone are available as parenteral formulations. Intravenous bolus morphine (initial analgesic effect in 5 minutes with a lag of peak effect to about 15–30 minutes) or methadone (2–5 minutes to effect) provide fast pain relief, and the use of patient-controlled analgesia devices help limit toxicity.[2,24,25] However, parenteral delivery of opioids for BTP is invasive, inconvenient, uncomfortable, and typically requires availability of continuous intravenous or subcutaneous access and relatively expensive and bulky delivery devices, which may not be available in community settings.

Recently, transmucosal (transbuccal, sublingual [SL], intranasal[IN]) delivery formulations have been developed for treatment of BTP. Transmucosal delivery has advantages of absorption into highly vascular areas which both produces rapid plasma levels of analgesics and bypasses hepatic metabolism, increasing bioavailability of medication. Such analgesic

products are more simple, convenient, and acceptable for treatment of BTP in community settings.

Oral Transmucosal Fentanyl Citrate

The first non-parenteral medication developed specifically for treatment of BTP in cancer patients on chronic opioid therapy was oral transmucosal fentanyl citrate (OTFC), approved by the Federal Drug Administration (FDA) in 1998 as Actiq® (Cephalon Corp.) Engineered using nanoparticle technology, this sweetened lozenge comes attached to a handle to enable patients to control the amount of medication absorbed through the oral mucosa.[26] Approximately 25% of the lozenge dose is absorbed directly into the mucosal venous complex, providing initial analgesia within 5 minutes, and peak effect at 40 minutes with the starting dose (200 μg) and 20 minutes with the highest dose (1600 μg).[26] The pharmacokinetics of OTFC are similar to the those of intravenous morphine and match the temporal characteristics of BTP better than the slower onset and prolonged duration of analgesia seen with oral immediate-release morphine. Of the approximately 75% of the total lozenge dose that is swallowed, one third (25%) escapes first pass hepatic metabolism and therefore approximately 50% of the total dose is bioavailable. The total duration of analgesia is approximately 1.5–3 hours and depends upon the amounts of fentanyl absorbed from the transmucosal and intestinal routes and the rate of predominantly hepatic metabolism.[26] The amount absorbed from each dose remains stable over multiple administrations and this along with its short half-life reduces the potential for accumulation of drug with repetitive dosing. Based upon small comparisons of healthy younger and older adults, age does not appear to alter the pharmacokinetics of OTFC metabolism.[27]

Published studies of OTFC for BTP include titration studies, randomized controlled effectiveness trials, and non-randomized studies. Two randomized, double-blind dose titration studies of OTFC in opioid-tolerant cancer patients showed that approximately 75% of the combined 127 patients were able to achieve a safe and effective dose of OTFC, with a mean successful dose of 600 μg.[28,29] Of note, no relationship was found between the effective dose for BTP and the total daily dose of opioids used for background pain, emphasizing the importance of individualized titration of OTFC dose rather than calculating doses as some proportion of the total daily opioid use. In a multicenter randomized, placebo-controlled trial of 92 opioid-tolerant cancer patients, OTFC was rated significantly better than placebo at reducing pain intensity at 15, 30, 45 and 60 minutes after consumption, and significantly better than placebo at reducing pain intensity.[30] Patients receiving OTFC also required significantly fewer doses of rescue medication for BTP compared with treatment with placebo. In 75 evaluable opioid-tolerant cancer patients, a randomized, double-blind crossover comparison of OTFC and immediate-release oral morphine at doses titrated to relieve BTP showed that OTFC significantly reduced pain intensity and improved pain relief compared with morphine at these same time points after administration.[31] Importantly, OTFC significantly relieved more pain episodes (defined as decrease in pain score by ≥33%) at 15 minutes than did morphine, and 94% of patients who chose to enroll in an subsequent open-label study wished to continue OTFC, whereas only 6% preferred immediate-release morphine.[31] An open-label study following 155 opioid-tolerant cancer patients who were successfully titrated to an effective dose of OTFC showed effectiveness in reducing pain in approximately 92% of episodes of BTP, with no need for dose escalation over time in 61% of patients.[32] In another smaller open label study in opioid-tolerant cancer patients, 42 of 57 patients (74%) titrated to an effective dose of OTFC, and among these, OTFC treatment significantly reduced BTP at 15, 30, 45 and 60 min after use compared with the patient's conventional medications (predominantly morphine).[33] A small retrospective chart review of the efficacy of OTFC in management of outpatient BTP crises in 39 opioid-tolerant cancer patients showed significant reduction in pain intensity and reduction in need for utilization of healthcare resources (urgent care visits and hospitalizations) and parenteral opioids.[34] Adverse events reported in <10% of patients were typical of opioid therapy, including somnolence, constipation, nausea, dizziness, and vomiting, with ≤5% of patients discontinuing therapy due to adverse events.[28,29,31,32] Specific side-effects of OTFC have been minimal but include increased dental decay, occasional delay in absorption and limited compliance in debilitated patients.[35] Although most

studies excluded cancer patients with active mucositis, one small study demonstrated tolerability of OTFC in head and neck cancer patients with active oral mucositis.[36] Based upon these data and the conclusions of a Cochrane review,[37] OTFC has been included in recommendations by the European Association for Palliative Care[4] and the National Comprehensive Cancer Network[20] for treatment of BTP in patients who have control of their background pain with oral opioids. Of note, OTFC is currently much more expensive than traditional opioid therapies, with price for the starting dose (200 μg) averaging $38 (U.S. dollars) at time of publication.[38]

Fentanyl Buccal Tablet

The fentanyl buccal tablet (FBT; *Fentora*™, Cephalon, Inc.) was approved by the FDA in September 2006 for treatment of BTP in opioid-tolerant (use of ≥60 mg oral morphine per day or equivalent opioid dose) patients with cancer. FBT is formulated to produce an effervescent reaction that alters the local salivary pH both to facilitate solubilization and to increase absorption of un-ionized fentanyl across the buccal mucosa.[39] Studies of pharmacokinetic properties in healthy, non-opioid tolerant adults showed rapid absorption with maximal plasma concentrations attained in 25–47 minutes.[35] Comparison of FBT and OTFC in these volunteers showed that FBT had more rapid absorption and higher maximal serum concentrations than OTFC, presumably due to the nearly equal proportions of FBT absorbed from buccal mucosa and the gastrointestinal tract, whereas 78% of the OTFC dose was absorbed from the gastrointestinal tract and was metabolized by the liver.[35,40] Notably, healthy subjects showed significant inter-individual variability in plasma half-life, especially at higher doses, ranging from 1–5 hours to 14–32 hours.

The therapeutic efficacy of FBT for treatment of BTP in opioid-tolerant cancer patients was evaluated in two randomized, double-blind placebo controlled trials.[41,42] In the first study of 123 opioid-tolerant adults with BTP from cancer (excluding those with intrathecal opioid therapy and moderate-to-severe mucositis or stomatitis, as well as those with sleep apnea, active brain metastases with increased intracranial pressure, chronic obstructive pulmonary disease, impaired renal or hepatic function, or significant bradyarrhythmia due to underlying heart disease), 46 patients (36%) discontinued the trial during the titration phase, 20 (16%) due to an inability to titrate to a dose effective for treatment of BTP.[41] For the 77 patients randomized in the trial, FBT was significantly superior to placebo in reducing pain intensity at all time points (15 to 60 minutes after use) and in reducing the need for supplemental analgesia.[41] As with OTFC, the effective dose of FBT was not correlated with the total 24-hour analgesic opioid use, again indicating the importance of dose titration when using these medications. In a second study using similar inclusion and exclusion criteria (except that patients with mucositis and stomatitis were permitted), 125 opioid-tolerant adults with cancer were titrated on FBT prior to randomization to treatment or placebo. Of these, 38 patients (30%) discontinued prior to randomization, 8 patients (6%) due to lack of efficacy.[42] For the 78 patients evaluable in the trial, FBT was significantly superior to placebo in reducing pain intensity from both nociceptive, neuropathic, and mixed pain from 10 minutes through two hours after treatment.[42] In addition, need for supplemental analgesia was significantly reduced after FBT compared with placebo. Adverse events typical of opioids were reported in 66% of patients, without any serious adverse events. Patient completing these two trials were rolled-over into an open-label safety trial[43] of long-term (≥12 months) FBT for BTP in 197 opioid-tolerant cancer patients. Adverse events typical of opioid treatment (nausea, constipation, dizziness, and somnolence) were reported in 38% of patients, with application site adverse events in 10 patients during the study, but no serious adverse events related to FBT occurred during the trial. However, in September 2007 the FDA issued a Public Health Advisory and a Healthcare Professional Sheet warning serious side effects including death in patients who have taken FBT.[44] This warning describes reports of prescribing to non-opioid-tolerant patients, misunderstanding of dosing instructions, or inappropriate substitution of FBT for OTFC by pharmacists and prescribers (not taking into account the higher bioavailability of FBT). Therefore, providers and patients are cautioned to follow directions for using FBT exactly, especially when converting from OTFC, to prevent death or other severe side effects from fentanyl overdose. In addition,

providers should note that FBT is significantly more expensive than conventional opioid formulations, comparable in price to OTFC.

Fentanyl Buccal Soluble Film (FBSF)

The BioErodible MucoAdhesive (BEMA™) delivery system was developed to facilitate reliable transmucosal delivery of drugs and improve patient acceptability. The fentanyl buccal soluble film (FBSF) system incorporates the opioid into a the active layer of a dime-sized bilayer patch, which is placed within the mouth and adheres to the mucosa. The active layer is covered by the inactive layer, which protects fentanyl from oral saliva and ensures more reliable transmucosal absorption. One small published trial of 12 healthy adults showed faster and greater peak and overall plasma concentrations after administration of FBSF compared with OTFC.[45] Presentations at scientific meetings reported the safety and effectiveness of FBSF (compared with placebo) in relieving BTP at 15 through 60 minutes after administration in opioid-tolerant cancer patients.[46,47] A recent publication (in press) of a multicenter, randomized, double-blind, placebo-controlled, multiple-crossover study of 80 opioid-tolerant cancer patients showed statistically significant relief of BTP from FBSF compared with placebo from 15 minutes through 60 minutes after administration.[48] FBSF treatment was not associated with any unexpected adverse events. Based on these data, the FDA approved FBSF as Onsolis® (BioDelivery Sciences International Inc) in June 2009 under a Risk Evaluation and Mitigation Strategy.

Emerging Pharmacologic Treatments for BTP

Sublingual opioid formulations

A new SL fentanyl tablet (available as Abstral™, Orexo and ProStrakan Group, in Europe and pending FDA approval in 2010 in the U.S.) has been formulated to optimize exposure of fentanyl to oral fluids and mucosa in combination with mucosal bioadhesion.[49,50] This product has been shown in small pilot studies to attain measurable plasma concentrations in 8–11 minutes,[49] and to reduce intensity of BTP within 15 minutes.[50] In a recent randomized, double-blind placebo-controlled multicenter trial of SL fentanyl in131 adults with cancer, 61 patients (46%) completed a titration phase and were evaluable.[51] Compared with placebo, SL fentanyl significantly relieved BTP at 10 minutes after administration and throughout the next hour. The pattern of adverse events was consistent with that previously reported for fentanyl. A recent publication of a case series showed the feasibility of using SL injection of the intravenous formulation of fentanyl for relief of BTP,[52] and the safety and efficacy of a SL fentanyl spray is under evaluation.[53] A recent reformulation of morphine tablets produces an easily digested effervescent solution when placed in water, that has been shown in one open-label study to have

Table 1. Established and emerging pharcotherapies for cancer-related BTP.

Treatment	Doses (µg)	Studies referenced
Current therapies		
Oral transmucosal fentanyl citrate (OTFC)	200*, 400, 600, 800, 1200, 1600	28–34
Fentanyl buccal tablet	100*,¶, 200, 300, 400, 600, 800	41–43
Fentanyl buccal soluble film	200*, 400, 600, 800, 1200	45–48
Emerging therapies		
Sublingual fentanyl tablet		49–51
Sublingual fentanyl spray		
Morphine effervescent tablets		
Intranasal fentanyl (sufentanil, alfentanil)		59–61,63
Subcutaneous injection pens		65
Nebulized fentanyl		60
Nitrous oxide		66

*indicates recommended starting dose; providers should initiate treatment at this dose and titrate up to effective dose, rather than choosing dose based on estimated equianalgesic effect.

¶see manufacturer recommendation for patients previously taking OTFC.

equivalent efficacy but significantly shorter time to pain relief than immediate-release oral morphine (13 versus 27 minutes) with equivalent side-effects.[54]

Intranasal opioid formulations

Intranasal (IN) opioids have several advantages over other routes of delivery. IN administration produces rapid onset of action equivalent to intravenous delivery[55] and shorter duration of effect by providing direct absorption of opioids into the vast and accessible nasal mucosal vascular complex.[56] Because they bypass the oral/gastrointestinal route, IN opioids could be particularly useful for patients with nausea or vomiting, with oral mucositis, or with decreased oral saliva.[56] IN morphine in doses up to 80 mg has been reported to provide relief of BTP within 5 minutes in uncontrolled open-label studies.[57,58] IN fentanyl (available in Europe as Instanyl®, Nycomed) has been used effectively for treatment of acute pain in emergency departments and in postoperative settings. Initial small pilot studies suggested the acceptability and effectiveness of IN fentanyl for treatment of BTP in cancer patients.[59,60] Recently, a larger randomized, double-blind, placebo-controlled crossover study evaluated IN fentanyl at doses from 50 to 200 µg in 111 opioid-tolerant cancer patients in intent-to-treat analysis.[61] Patients were excluded if they were pregnant or breast-feeding, had psychiatric, severe hepatic, or respiratory impairment, were actively treated with monoamine oxidase inhibitors, methadone, or buprenorphine, or were using other IN drugs. After successful titration to an effective dose of IN fentanyl, patients were followed for 3 weeks. During this efficacy phase, IN fentanyl produced significantly better pain relief at 10 minutes and better overall response at all time points up to 60 minutes compared with placebo, with better pain relief from 100 and 200 µg doses compared with 50 µg.[61] During the efficacy phase, 2 adverse events, including one accidental overdose, were considered related to study drug. In the subsequent 10 month open-label tolerability phase, most adverse events were related to progression of malignant disease, and 4.6% of patients had adverse events considered related to treatment, including one patient with epistaxis. Another recent study compared titration of IN fentanyl with OTFC in a multicenter open-label crossover trial of 139 opioid-tolerant cancer patients.[62] Compared with OTFC, time to meaningful pain relief was faster with IN fentanyl (median 11 minutes and 16 minutes, IN and oral transmucosal, respectively), and use of IN fentanyl was associated with significantly greater pain relief and higher patient preference.[62]

Because of their 10 times greater potency compared with fentanyl and 65%–70% bioavailability, sufentanil and alfentanil have potential to provide greater pain relief than fentanyl when delivered intranasally. A recent observational open-label study in 30 cancer patients with opioid-tolerant BTP showed that IN sufentanil rapidly relieved BTP within 15 minutes, with pain relief from an average 18 µg dose.[63] Few adverse events were seen in this small study; five patients withdrew from the study due to headache (n = 1), severe osteoarthritis limiting use of the device (n = 1), inadequate pain relief (n = 1), fall in respiratory rate from 20 to 16 (n = 1), and noncompliance (n = 1). At present, use of IN alfentanil has been reported only in one small study of analgesia in 36 children, for whom the medication appeared to be safe and effective.[64]

Subcutaneous injection of opioids with the "pain pen"

SC injections and continuous infusions have been widely used for years and are preferred by patients over IM injections and often over IV administration. Recently, preloaded injection pens, which are clinically available for administration of insulin and heparin, have been explored as alternative delivery devices for opioids in treating BTP. Injection pens are convenient and acceptable to most patients, and have the ability to deliver significantly larger volumes and doses of opioids compared to the limited amounts of opioid that can be delivered per dose with intranasal (approximately 0.2 mL) and sublingual (3 mL) routes. Two open-label pilot studies of opioid-tolerant adults with cancer have evaluated injection pens to deliver hydromorphone (43 patients), morphine (11 patients), or sufentanil (4 patients) for treatment of BTP over a median duration of 6 weeks.[65] The equianalgesic dose per injection was 25 mg SC morphine, in an average volume of 0.65 mL. Rapid pain relief was noted at 5–10 minutes, with effectiveness rated qualitatively as good in 84%, and moderate in 14% of patients.

Inhaled formulations

As a form of transmucosal delivery, inhaled therapies have the potential advantage of an immense vascular bed in the airways and lungs for rapid uptake of analgesia. Based on principles using inhaled opioids for postoperative pain, a series of case reports indicate benefit from nebulized fentanyl for BTP in cancer patients.[60] Larger systematic studies are needed, but it is worth noting that nebulized therapies are sometimes not accepted by patients as they are inconvenient, noisy and time-consuming.

An alternative inhaled analgesic, nitrous oxide is a weak anesthetic with analgesic and amnestic properties. Supplied as Entonox® (BOC group) or Nitronox® in a mixture of 50% NO and 50% O_2, nitrous oxide provides very rapid pain relief in a formulation that patients can self-administer using a facemask. Use of nitrous oxide is relatively safe but treatment can cause sedation and may exacerbate reactive airways disease in some patients. Nitrous oxide has been evaluated in a very small randomized double-blinded crossover study of 7 patients with terminal malignancy.[66] Comparison of mixtures of nitrous oxide/oxygen and air/oxygen showed that nitrous oxide tended to be associated with less incident pain, but no significant differences in overall pain scores or use of opioids could be demonstrated in this small study.[66] Further development of this therapy may provide a formulation that could be used in anticipation of predictable incident pain.

Use of N-Methyl-D-Aspartate (NMDA) antagonists

BTP, especially from neuropathic and bone pain, has been proposed to involve peripheral and/or central sensitization, mediated through activated NMDA receptors.[67] Consequently, the effects of the NMDA antagonist methadone in BTP have been evaluated in small studies.[2] Methadone is highly potent in opioid-tolerant cancer patients, is readily absorbed through the oral mucosa due to its lipophilic properties, and is inexpensive. A small open-label feasibility study of 7 cancer patients with BTP showed that sublingual methadone titrated to doses of 2–18 mg was tolerated with mild toxicity, and for the 4 patients studied at optimal dosing, effectively reduced BTP within 5 minutes.[68] Further research is needed to study the long-term use of repeated doses of methadone for treatment of BTP, especially given its unpredictable pharmacokinetics and cumulative effect of methadone.

Summary

Even when baseline cancer pain is controlled using conventional approaches to opioid therapy, the majority of patients experience daily episodes of breakthrough pain (BTP) at some point in their disease which significantly reduces their quality of life. Although some types of BTP can be anticipated and treated preemptively, many types of BTP are unpredictable, severe, sudden (with pain intensity peaking within minutes), and transient (lasting only 30–60 minutes). Optimal management of these kinds of BTP requires delivery of analgesics with rapid onset and short duration of effect, ideally in convenient and easily administered formulations. Most of the recently developed and emerging pharmacotherapies discussed in this review exploit the properties of transmucosal absorption of lipophilic opioids delivered using transbuccal, sublingual, and intranasal formulations in order to provide this rapid (onset within 5–15 minutes) and potent relief of BTP. In addition, the newer delivery systems are regarded by patients to be convenient and acceptable for treatment of BTP in community settings. However, these recently developed and emerging pharmacotherapies are at present and likely will be significantly more expensive than conventional oral opioid preparations, which may unfortunately limit their affordability for many patients. Providers who do use these analgesics are cautioned to carefully titrate from the recommended starting dose to an effective dose, rather than choosing a dose based on estimated equianalgesic effect, because of the unique properties of these new agents and the variable bioavailability of different formulations.

Disclosures

This manuscript has been read and approved by the author. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The author and peer reviewers of this paper report no conflicts of interest. The author confirms that they have permission to reproduce any copyrighted material.

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