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# Non pharmacological interventions and non-fentanyl pharmacological treatments for breakthrough cancer pain: A systematic and critical review

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ABSTRACT

Background: Oral opioids or other pharmacological or non-pharmacological interventions are often suggested in the management of breakthrough cancer pain (BTcP). The aim of this systematic and critical review was to analyse and critically comment the evidence of any non-fentanyl therapies proposed for BTcP.

*Methods:* A systematic literature search was carried out to find studies providing clinical data on any treatment excluding fentanyl products.

*Results:* No data exist about the use of oral opioids. Some information is available on parenteral morphine in a large sample of patients and episodes of BTcP. For other treatments, including methadone, nitrous oxide, anti-inflammatory drugs, samarium, and gabapentin the existing data, observational and obtained in a small number of patients do not provide useful information to be generalized. Only ketamine, a drug difficult to use for many physicians, particularly in determined setting, provided some evidence according a randomized controlled double-blind study.

*Conclusions:* Recommendations suggesting the use of oral opioids or other pharmacological and non-pharmacologic interventions for BTcP, are not based on any, even minimal evidence. These treatments are worthwhile of further investigation, particularly in determined conditions that should fit the pharmacokinetics of oral opioids.

## 1. Introduction

It has been recognized that cancer patients, despite having a well controlled background pain by an analgesic drug for most hours of the day, may experience acute painful episodes that are highly distressing. This phenomenon is commonly named breakthrough cancer pain (BTcP) (Mercadante and Portenoy, 2016). Non-pharmacological and pharmacological approaches have been invariably reported in literature. The role of primary therapies, including hormonal manipulation, chemotherapy, the use of orthotic devices or surgical stabilization, radiotherapy, and the use of bisphosphonates have obvious implications in preventing BTcP and may improve the quality of life, but they have never been investigated properly. Administration of analgesic drugs 'as-needed' is commonly suggested to manage episodes of BTcP. In particular, transmucosal fentanyl, that is a lipophilic drug, matches the characteristics to favour the passage through the mucosa and then across the blood-brain barrier to provide fast analgesia. All the studies performed with transmucosal fentanyl preparations, also named rapid onset opioids, suggest that this approach is more effective and rapid in comparison with oral opioids and placebo (Jandhyala et al., 2013; Mercadante, 2012). However, in many guidelines oral opioids or alternative non-pharmacological interventions are often reported (Anon, 2013; Daenick et al., 2006; NICE, 2017; Wengström et al., 2014). For example, the National Institute for Clinical Excellence (NICE) has issued a guideline indicating that oral morphine should be considered the first-line choice for BTcP (NICE, 2017). In United States, a prior treatment with oral opioids is required by much of the payer community before coverage for a transmucosal fentanyl preparation is provided (Mercadante and Portenoy, 2016). The aim of this systematic and critical review was to analyse and critically comment the evidence of any non-fentanyl therapies proposed for BTcP.

## 2. Methods

A systematic literature search on Pubmed, MedLine, and Embaseelectronic databases was carried out from each database text words and MeSH/EMTREE term was "breakthrough pain". Studies were selected if prospective, if they were performed in adult patients with chronic cancer pain, containing data about methods used for the management of BTcP, and written in English language. Treatments that

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excluded any fentanyl preparation were included. Only papers providing clinical data on BTcP episodes were included. Case reports or cases series with less than 20 episodes of BTcP were excluded.

## 3. Results

The initial search yielded 1354 records. Sixteen papers were fully examined after the initial screening according to inclusion and exclusion criteria. Six more studies were found through cross-references (Brogan et al., 2015; Fisher et al., 2004; Fitzgibbon et al., 2003; Freye et al., 2007; Hagen et al., 2007; Rauck et al., 2003). Of these, two papers assessing effectiveness of implantable pumps with a chance to activate drug delivery as needed for the management of cancer pain (Brogan et al., 2015; Rauck et al., 2003), were not considered because they did not report data on specific episodes of BTcP. Gabapentin and samarium infusion for bone incident pain were also used for BTcP, but no episode was evaluated as they were intended to prevent the phenomenon of BTcP, rather than treating the single episode (Caraceni et al., 2008; Ripamonti et al., 2007). One paper was the presentation of a trial of a project regarding a controlled study of inhalation of nitrous oxide (N2O) for the management of BTcP (Liu et al., 2017). Seventeen papers were analyzed for the review.

Six studies assessed alternative formulations of morphine and methadone (Fisher et al., 2004; Fitzgibbon et al., 2003; Freye et al., 2007; Hagen et al., 2007; Hagen et al., 2010; Pavis et al., 2002). Four observational studies assessed intravenous morphine, and one of them was controlled with a transmucosal fentanyl preparation (Mercadante et al., 2004a; Mercadante et al., 2006; Mercadante et al., 2007; Mercadante et al., 2008). In one study, intravenous patient-controlled analgesia with different opioids, including morphine, fentanyl, and methadone, was used for the management of BTcP (Sousa et al., 2014). In another controlled study, fixed doses (5 mg) of subcutaneous morphine were compared with sublingual fentanyl 100 mcg for the management of BTcP (Zecca et al., 2017).

Studies of non-opioid drugs included two small series regarding the use of N2O (Enting et al., 2002; Keating and Kundrat, 1996), and a controlled study of a non-inflammatory drug and oral morphine (Hao et al., 2013).

Ketamine was assessed in a small series of patients with difficult pain syndromes receiving spinal analgesia (Mercadante et al., 2005). Only one randomized placebo-controlled crossover study of ketamine in a mixed population of cancer and non cancer patients was found (Carr et al., 2004).

Spinal analgesia with boluses of local anesthetics was reported in one study (Mercadante et al., 2005).

No study assessed alternative or non-pharmacological treatments of breakthrough pain.

## 4. Discussion

In the last decades industries gave the input for numerous studies assessing the efficacy of fentanyl preparations, characterized by a rapid onset and a short duration of action, in an attempt to overlap the temporal profile of BTcP. Randomized-controlled studies have shown their efficacy and superiority over placebo and oral opioids (Jandhyala et al., 2013; Mercadante, 2012; Zeppetella et al., 2014). However, many concerns have been raised, particularly regarding the costs. Oral opioids have been widely used and are still considered the first choice (NICE, 2017). Moreover, other approaches have been proposed, including pharmacological and non pharmacological methods. This review underlines how these assumptions are not based on any evidence or even minimal anecdotal experience. No study regarding oral morphine has even been published, even small observational series. Indeed, data of poor quality have been invariably produced on alternative formulations of morphine and methadone.

### 4.1. Oral or alternative formulations of opioids

To achieve rapid absorption and onset of effect, a fixed dose of 40 mg of nasal morphine gluconate was given to 11 patients for BTcP to evaluate pharmacokinetic, safety, and efficacy. The time to perceptible pain improvement was a mean of 2.2 min. Only five patients experienced meaningful pain relief in a mean of 9.1 min, but 72% of patients required a rescue medication (Fitzgibbon et al., 2003). Effervescent morphine has been produced to facilitate intestinal absorption rate of oral morphine. Tablets of effervescent morphine were given to 76 cancer patients for BTcP, in doses of 10–80 mg, similar to those used with previous traditional oral morphine. The onset of sufficient pain relief was half of that reported with traditional oral morphine, although it was unclear what was sufficient pain relief. Historical data regarding traditional oral morphine were used for comparison, and patients were already responsive to oral morphine, as it occurs in an enrichment study. Moreover the effervescent formulation may provide more expectations that could explain the shorter onset of action. Also, it was unclear why effervescent morphine would reduce the number of episodes of BTcP (Freye et al., 2007). Nasal morphine combined with chitosan, a bioadhesive substance that allows more time for absorption, slowing the mucociliary clearance, was assessed. Its efficacy and tolerability were assessed in 20 episodes in 14 patients. Pain intensity was reported by a verbal scale (Pavis et al., 2002). No further studies confirmed this data.

In a pilot study 37 episodes of BTcP in six patients were treated with starting doses and optimal doses of methadone, after dose titration, of 1–15 mg and 2–15 mg, respectively. The onset of analgesia occurred by 10 min after ingestion, but data were lacking for half patients at day 4 and 5. No relevant differences between patients' usual BTcP medication and optimal dose of methadone, were noticed. Adverse effects included dry mouth, drowsiness, and dizziness (Fisher et al., 2004). In a feasibility study, sublingual methadone was given on 83 episodes of BTcP. Doses were titrated to achieve the optimal doses starting with 2 mg. Of eighteen patients, only five patients were successfully titrated, and 84 episodes of BTcP were evaluable. Optimal dose was highly variable (2–30 mg). Pain intensity decreased by 1.7 and 3.2 points, 10 and 15 min after sublingual administration of methadone, respectively. Considering the amount of rescue opioid doses previously used, it is likely that these patients had their background pain uncontrolled (Hagen et al., 2010). Sixty-one episodes in 7 patients were evaluated with sublingual methadone at escalating doses ranging 8–18 mg. Four of seven patients entered the optimal dose evaluation phase, and 39 episodes could be evaluated. A significant pain reduction occurred within 5 min and no relevant adverse effects were observed (Hagen et al., 2007). Indeed, the pharmacokinetics of methadone does not suggest to use this drug for repeated episodes of BTcP. Methadone, despite having a shorter onset of action, unfits the profile of a BTcP event and possibly may produce accumulation of the drug whether repeated during the day. The poor assessment, the low number of episodes assessed, and quality of data do not allow to draw useful information for both alternative morphine formulation and methadone.

Thus, despite in many guidelines and recommendations oral opioids, particularly morphine, still remain the drug of choice for the management of BTcP (NICE, 2017), this statement is not supported by any existent study, neither open label or controlled. No study has never assessed the efficacy of oral morphine for the management of BTcP, regardless of its traditional use for decades. It is surprising and possibly due to poor commercial interest by industries. On the other hand, several surveys have demonstrated that most BTcP episodes have a short onset (few min) and persist for 30–60 min. This time course has little in common with the typical pharmacokinetic-pharmacodynamic relationship of an orally-administered opioid drug such as morphine, which has an onset in 30–45 min, a peak effect that may occur an hour or more later, and a duration of 3–4 h (Zeppetella et al., 2014). This mismatch between the most prevalent time course of BTcP and the