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ORIGINAL ARTICLE

The efficacy of oral piroxicam fast-dissolving tablets versus sublingual fentanyl in incident breakthrough pain due to bone metastases: a double-blinded randomized study

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Abstract

Purpose Breakthrough pain (BTP) is a transient exacerbation of pain occurring in a patient with chronic, persistent pain. The most common type is incident pain that is mostly related to bone metastases. The oral mucosa is an attractive route for drug delivery. Sublingual fentanyl preparations are a very attractive agent in controlling attacks of BTP due to its rapid absorption through the oral mucosa. Non-steroidal anti-inflammatory drugs (NSAIDs) play a key role as a first step in treatment of cancer pain; piroxicam sublingual formulations could be a useful alternative in controlling *incident* pain. Our study hypothesis is to evaluate the efficacy of sublingual fentanyl versus oral piroxicam fast-dissolving tablets in patients with incident pain and its impact on functional status.

Patients and methods A cohort of 100 adults of both genders suffering from bone metastases. Patients were assigned to receive either sublingual fentanyl tablet (*group 1*) or oral piroxicam fast-dissolving tablets (*group 2*). The pain intensity reduction on a 0–10 visual analog scale (VAS), frequency of BTP attacks, and onset of pain relief. Secondary end points included the functional interference items of the Brief Pain Inventory (BPI).

Results There is no significant difference between the two groups regarding the patients' demographics. Significant decline of the VAS in each group in comparison to the pretreatment values ($p = 0.001$). Non-significant changes of the VAS, duration of pain attacks, and number of rescue doses in comparing both groups were measured. There was significant reduction in group 2 BPI regarding the relation with others, sleep pattern and enjoyment of life parameters at 2 and 4 weeks ($p = 0.001$).

Conclusion Our study demonstrated that oral piroxicam fast-dissolving tablet is an analgesic alternative to sublingual fentanyl in patients with bone metastasis to control incidental BTP attacks with more favorable cost-benefit values.

Keywords Oral piroxicam tablets · Sublingual fentanyl · Incident BTP · Bone metastases

Introduction

The term of breakthrough pain (BTP) is considered as transient exacerbation of pain in patients with persistent chronic pain. It affects more than 60% of cancer patients, particularly those with moderate to severe chronic pain. It is a resistant type of pain syndromes for management. There are multiple forms of BTP cancer pain [1]. The most common type of BTP in cancer patients is incident pain that is mostly related to bone metastases [2].

The oral mucosa is an attractive route for drug delivery as it is generally associated with more rapid absorption compared with the oral route [3]. Fentanyl is a highly lipophilic opioid and, when placed in saliva under normal oral conditions, 80% of the administered dose remains non-ionized allowing the drug to pass readily through the buccal mucosa, quickly cross the blood–brain barrier, and enter the central nervous system [4].

Poor economy, relatively high cost of rapidly acting opioid in developing countries, in addition to lack of pharmacoeconomic studies assessing the net benefit of different formulation of rapidly acting opioid, directed the health care directors to seek alternative measures to control BTP attacks at relatively low cost with nearly similar efficacy to sublingual rapidly acting opioid [5, 6].

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Non-steroidal anti-inflammatory drugs (NSAIDs) play a key role as a first step in treatment of cancer pain, nearly 90% of patients with bone metastasis present with pain. Prostaglandins appear to play an important role in incidental pain management. Particular fast-released, sublingual formulations of NSAIDs are useful alternative in controlling incidental pain. Piroxicam inhibits arachidonic acid from converting to prostaglandin endoperoxide, thus having a pivotal role in cancer pain management [7].

The aim of this study is to determine the long-term efficacy, tolerability, and patient satisfaction of sublingual fentanyl versus oral piroxicam fast-dissolving tablets in the management of BTP and its impact on quality of life and functional status.

Patients and methods

Protocol of the study

The study was approved by an Investigational Review Board of the Faculty of Medicine, Tanta University; an informed written consent was obtained from all patients participating in the study. This study was registered in the clinical trials registry (clinicaltrials.gov) with a unique identification number NCT02382653.

A cohort of 100 adults of both genders suffering from cancer pain with bone metastases whose background pain was treated according to the World Health Organization (WHO) analgesic ladder. BTP attacks were stable under analgesia in the previous 48 h, controlled background pain in the previous 24 h, and transient exacerbation of pain in the previous 24 h.

The primary tumor sites were as follows: breast, 30 patients; lung, 19 patients; liver, 15 patients; gastrointestinal cancer, 8 patients; prostate cancer, 14 patients; pancreatic tumor, 10 patients; and thyroid carcinoma, 4 patients. The most common sites of metastasis are long bone, 37; spine, 21; hip joint, 13; ribs, 14; and disseminated metastases in 15 patients.

Exclusion criteria were less than 18 years old, non-controlled basal pain, hospitalized patients or patients with history of cognitive disturbances, patients with contraindication to NSAIDs such as gastric ulcer, impaired renal function, cerebrovascular accident, coronary artery bypass graft, and uncontrolled hypertension, patients with coagulation anomalies such as hepatic disease, or patients with previous history of allergy to NSAID.

Patients were randomly allocated into both groups: patients were assigned to receive either sublingual fentanyl tablet 200 μg [8] (*ProStrakan Ltd, Gala Bank Business Park, Galashiels, UK*) (*group 1*) or oral piroxicam fast-dissolving tablets 20 mg (*Feldene Flash, Pfizer Inc., New York, NY, 10017, USA*) (*group 2*), 50 patients in each group (Fig. 1).

Randomization was performed by random numbers using sealed envelopes without sex stratification. Sealed envelope indicates the group assignment. An independent pain physician, who did not participate in the study design or data collection, red the number contained in each envelope and made group assignments. Sublingual fentanyl tablets were packaged in group-specific bottles and coded as G1 bottle (*group 1*); oral piroxicam fast-dissolving tablets were packaged in identical bottles and coded as *G2* bottle (*group 2*). Only the hospital pharmacist knows the meaning of these key letters and disclosed only after completion of the study. Patients were blindly randomized into two groups: the process of inclusion into the study gone on until the requested number of patients was reached. The process of inclusion started at the pain relief outpatient clinic of Tanta University Hospitals in December 2014 until May 2015.

Doses were adjusted individually and the dose was titrated over 2-week period to find the dose with the optimum efficacy, effectiveness in reducing the intensity and/or frequency of movement-related volitional incident pain [6], and minimal adverse events. The "effective dose" was defined as the dose needed to control BTP (pain reduction by 50% in each pain episode without the occurrence of relevant adverse events). If the pain persists for more than 30 min, the next dose is administered. Patients failed to achieve an effective dose after the third rescue dose; their background narcotic was readjusted.

The pharmacist in duty of the pain clinic repacked the rescue drugs in identical bottle and relabeled it as G1 for fentanyl and G2 for piroxicam. The pain clinic physician assessing the degree, duration, and number of rescue doses was unaware of the types of rescue drugs were given.

The primary measure was pain intensity reduction on a 0–10 visual analog scale (VAS), frequency of BTP attacks throughout the day, and onset of pain relief. Secondary end points included the functional interference items of the Brief Pain Inventory (BPI). The BPI is a reliable pain assessment tool for use in patients with cancer. It measures the intensity of pain, in addition to interference of pain in the patient's life. It also queries the patient about pain relief, pain quality, and patient perception of the cause of pain [9].

Data collection forms

Patients instructed to complete a daily diary throughout the study. The diary identifies the total intake of analgesia, the worst pain recorded during the pain attacks, the frequency of BTP attacks, and the onset of pain relief, in addition to the items of other items of the BPI. All outcomes were assessed at 3, 7, 15, and 30 days after starting the treatment by the pain physician who is completely blinded to the study design and did not participate in the study or data collection.

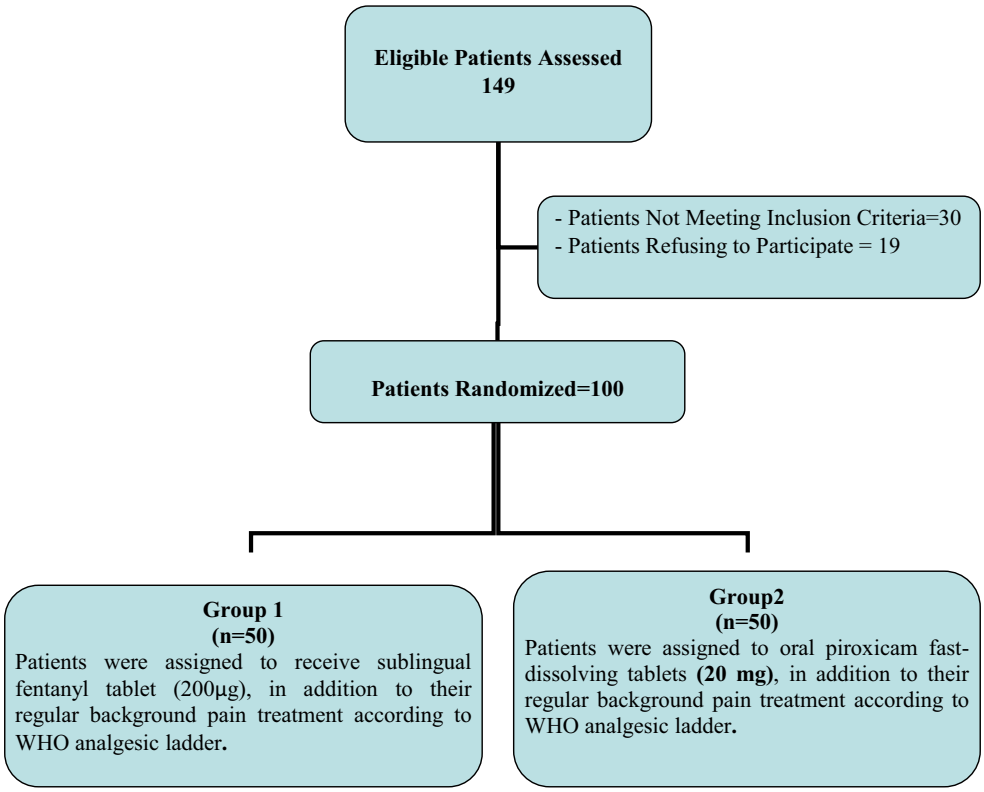

Fig. 1 Patient flow throughout the study

Sample size analysis

A sample size analysis determined that $n = 46$ patients per group are required to detect difference of at least 20% reduction in the VAS between groups with a power of 80%, α of 0.05, and allocation ratio of 1:1 using a 95% confidence interval and allowing for a 10% attrition/non-compliance rate (nQuery Advisor, Version 5.0; Statistical Solutions, Saugus, MA, USA), so we included 50 patients per group.

Statistical analysis

The collected data were organized, tabulated, and statistically analyzed using SPSS version 19 (Statistical Package for Social Studies) created by IBM, Illinois, Chicago, USA. For numerical values, the range mean and standard deviations were calculated. The differences between the mean values between the two studied groups at each period of follow-up were used using student's *t* test. For comparison of the mean values within each group at different periods of follow-up, repeated measurement analysis of variance test was used and Bonferroni test was used to compare each tow mean values. For categorical variable, the number and percentage were calculated and differences between subcategories were tested, Fisher's or Monte Carlo exact test. The level of significance was adopted at $p < 0.05$.

Results

There is no significant difference between the two groups regarding the patients' demographics. The onset of pain relief in group 1 is significantly rapid in comparison to group 2 ($p = 0.001$) (Table 1).

Comparison of the VAS within each group revealed significant decline of the VAS in each group throughout the study period in comparison to the pretreatment mean value ($p = 0.001$). Comparison of the VAS between both groups revealed non-significant changes of the VAS in comparing both groups throughout the study period (Table 2).

Changes in the functional capacity of the BPI in both groups revealed significant reduction in all components of the BPI in both groups in comparison to the pretreatment mean values. Comparing both groups revealed significant reduction in the group 2 mean values regarding the relation with others, sleep pattern and enjoyment of life parameters at 2 and 4 weeks in comparison to the mean values in group 1 ($p = 0.001$) (Table 3).

Table 1 Patient characteristics in the studied groups

	Group 1 ($n = 50$)	Group 2 ($n = 50$)	T or X^2	p
Age (years) Mean (range)	55.06 ± 9.38 (39–78)	53.44 ± 7.34 (39–70)	0.962	0.339
Gender				
Male	31 (62%)	28 (56%)	3.252	0.071
Female	19 (38%)	22 (44%)		
Height in cm	162.88 ± 9.58	162.66 ± 8.64	0.121	0.904
Weight in Kg	76.38 ± 7.25 (63–95)	77.46 ± 8.24 (63–94)	0.696	0.488
Primary cancer site				
Breast	16	14	MCET	0.840
Lung	8	11		
HCC	9	6		
GIT carcinoma	5	3		
Prostate cancer	6	8		
Pancreatic tumor	4	6		
Thyroid	2	2		
Site of metastases				
Long bone	18	19	0.541	0.969
Spine	11	10		
Hip joint	6	7		
Ribs	8	6		
Disseminated	7	8		
Onset of pain relief				
Mean ± SD	6.10 ± 1.23	17.14 ± 3.76	36.308	0.001
Range	(3–8)	(14–21)		

MCET Monte Carlo exact test

Comparison of the mean duration of BTP attacks within each group revealed significant decline of the mean duration in each group throughout the study period in comparison to the pretreatment mean value ($p = 0.001$). Comparison of the mean duration between both groups revealed non-significant changes of the mean duration in comparing both groups throughout the study period (Table 4).

Comparison of the mean number of rescue doses within each group revealed significant decline of the mean number of rescue doses in each group throughout the study period in comparison to the pretreatment mean value ($p = 0.001$). Comparison of the mean number of rescue doses between both groups revealed non-significant changes of the mean duration in comparing both groups throughout the study period (Table 5).

Discussion

This study is, to our knowledge, the first to compare the analgesic efficacy of oral piroxicam fast-dissolving tablets versus sublingual fentanyl in cancer BTP in patients with bone metastases. Our study demonstrated significant reduction of pain score, incidence and duration of BTP attacks, and significant improvement in most of the elements of functional status of the BPI during the 4-week follow-up period in both groups. Our study revealed that of oral piroxicam fast-dissolving tablet is an equivalent analgesic alternative to sublingual fentanyl in cancer BTP due to bone metastases.

The buccal and sublingual tissues are the primary focus for drug delivery via the oral mucosa because they are more permeable than the tissues in the other area of the mouth. The mucosa is easily accessible, convenient, noninvasive, and less threatening to patients compared to other routes of administration such as intravenous or intramuscular. Furthermore, it does not require a technical equipment, expertise, preparation, and supervision. The buccal mucosa is highly vascularized and therefore any drugs diffusing into the oral mucosa membranes have direct access to the systemic circulation via capillaries and venous drainage. Drugs are absorbed through the oral mucosa directly into the systemic circulation [10].

Tumor metastasis to bone is associated with bone destruction and new bone formation, and prostaglandin biosynthesis appears to be an integral part of this process [11]. Yalcin et al. [12] studied a total of 21 patients with cancer. The mean VAS scores were statistically lower after a single dose of 20 mg

Table 2 Comparison of the mean value of the VAS between the studied groups

VAS	Group 1 ($n = 50$)	Group 2 ($n = 50$)	T	p
Pretreatment (mean ± SD)	8.09 ± 0.8062	8.3 ± 0.75	1.344	0.182
3 days (mean ± SD)	6.81 ± 0.82	6.82 ± 0.81	0.061	0.951
1 week (mean ± SD, range)	5.62 ± 0.91	5.66 ± 0.099	0.209	0.835
2 weeks (mean ± SD)	4.43 ± 0.82	4.6 ± 0.85	1.009	0.315
3 weeks (mean ± SD)	3.94 ± 0.78	3.97 ± 0.74	0.197	0.845
1 month (mean ± SD)	3.37 ± 0.74	3.47 ± 0.76	0.661	0.510
F	259.617	429.206		
p	0.001	0.001		

Bonferroni test: group 1, baseline significantly different from all measures at follow-up and each measure at follow-up significantly different from other measures. Group 2, baseline significantly different from all measures at follow-up and each measure at follow-up significantly different from other measures

Table 4 Comparison of the mean duration of breakthrough pain attacks in the studied groups

Duration of attacks	Group 1 ($n = 50$)	Group 2 ($n = 50$)	T	p value
Pretreatment (mean ± SD)	46.96 ± 7.3	45.12 ± 6.91	1.294	0.199
After 2 weeks (mean ± SD)	36.1 ± 6.45	34.25 ± 5.99	1.685	0.095
After 4 weeks (mean ± SD)	21.74 ± 5.34	22.16 ± 4.97	0.407	0.685
F	503.346	337.585		
p	0.001	0.001		

Bonferroni test: group 1, baseline significantly different from all measures at follow-up and each measure at follow-up significantly different from other measures. Group 2, baseline significantly different from all measures at follow-up and each measure at follow-up significantly different from other measures

piroxicam sublingually. Complete relief was achieved in three patients 14% and partial relief was detected in four (19%). All patients achieved 33% pain relief and tolerated the sublingual piroxicam very well without any significant side effects.

NSAIDs are sometimes used by patients to treat BTP episodes [13, 14]. Interestingly, over 35% of the patients included in the study of Janecki et al. [15] were using formulations of NSAIDs as rescue medications for BTP. The results clearly confirmed that patients do not take opioid rescue medication every time they experience BTP episode. The most common reasons for not taking rescue medication that pain improved before the drug started to work in addition to low pain intensity. This second reason mostly explaining why patients not using the opioid rescue medication or taking non-opioid NSAIDs. Moreover, the majority of patients mentioned that their management of BTP is effective.

Sublingual fentanyl tablet contains water soluble formulations that are coated with fentanyl covered by a mucoadhesive agent to hold the tablet under the tongue [16]. Sublingual administration of fentanyl provides a noninvasive mechanism for faster absorption and a more effective onset of pain relief.

Table 3 Changes in the functional capacity of the Brief Pain Inventory in the studied groups

BPI item	Pretreatment		2 weeks		4 weeks			
	Group 1 ($n = 50$)	Group 2 ($n = 50$)	Group 1 ($n = 50$)	Group 2 ($n = 50$)	Group 1 ($n = 50$)	Group 2 ($n = 50$)	$p^{\dagger}$	$p^{\ddagger}$
General activity (mean ± SD)^{P}	7.97 ± 0.82	7.6 ± 0.808 0.26	6.02 ± 0.82	5.80 ± .808 0.180	3.58 ± 1.18	3.45 ± 0.87 0.516	0.001	0.001
Mood (mean ± SD)^{P}	6.81 ± 0.94	6.72 ± 1.08 0.659	4.78 ± 1.06	4.84 ± 1.04 0.776	3.1 ± 0.86	2.94 ± 0.95 0.383	0.001	0.001
Walking ability (mean ± SD)	6.82 ± 0.82	6.38 ± 1.68 0.214	4.86 ± 1.61	4.59 ± 1.41 0.377	3.05 ± 1.2	2.8 ± 1.08 0.283	0.001	0.001
Normal work (mean ± SD)	7.54 ± 0.01	7.39 ± 1.2 0.503	5.79 ± 1.04	5.35 ± 0.89 0.25	4.29 ± 0.86	3.98 ± 0.74 0.059	0.001	0.001
Relation with others (mean ± SD)	6.2 ± 0.95	5.52 ± 0.942 0.069	5.03 ± 0.73	4.5 ± 0.58 0.001	4.22 ± 0.53	3.73 ± 0.52 0.001	0.001	0.001
Sleep (mean ± SD)	5.8 ± 0.73	5.6 ± 0.67 0.16	4.93 ± 0.76	2.96 ± 0.49 0.001	3.91 ± 0.67	2.56 ± 0.51 0.001	0.001	0.001
Enjoyment of life (mean ± SD)	6.34 ± 0.95	5.96 ± 0.86 0.42	5.32 ± 0.89	4.36 ± 0.72 0.001	4.20 ± 0.83	3.26 ± 0.8 0.001	0.001	0.001

Bonferroni test: group 1, baseline significantly different from all measures at follow-up and each measure at follow-up significantly different from other measures. Group 2, baseline significantly different from all measures at follow-up and each measure at follow-up significantly different from other measures

$^{\dagger}p$ value within group 1

$^{\ddagger}p$ value within group 2

^{P}p value between groups

Table 5 Comparison of rescue doses in the studied groups

Duration of attacks	Group 1 ($n = 50$)	Group 2 ($n = 50$)	T	p value
Pretreatment (mean ± SD)	3.20 ± 0.571	2.82	1.294	0.199
After 2 weeks (mean ± SD)	2.34 ± 0.519	2.06	1.685	0.095
After 4 weeks (mean ± SD)	1.56 ± 0.501	1.34	0.407	0.685
F	211.830	159.627		
p	0.001	0.001		

Bonferroni test: group 1, baseline significantly different from all measures at follow-up and each measure at follow-up significantly different from other measures. Group 2, baseline significantly different from all measures at follow-up and each measure at follow-up significantly different from other measures

As it is highly lipophilic, fentanyl easily crosses the blood–brain barrier and its absorption through the buccal mucosa is gradual and predictable [17].

This systemic thereby achieves the optimal exposure of the active substance, in quantity and time, and the drug can be detected in plasma in 8–11 min, with low inter-individual variability and linear pharmacokinetics at the doses studied and an estimated onset of action of 5–15 min [18]. Previous studies [4, 19, 20] assessed the efficacy of sublingual fentanyl tablet in BTP and their findings provided significant improvements in pain relief and reduction in pain intensity scores with an acceptable safety profile confirmed in the long-term follow-up. Improvement in patients' quality of life with sublingual fentanyl tablet was reported in addition to high levels of satisfaction [21]. Patients treated with sublingual fentanyl to treat cancer BTP were effective and safe in multiple studies [22, 23].

Multiple problems facing proper cancer pain management in developing countries where there are problems of poor economy, absence of effective national health insurance schemes, poor drug storage conditions, adverse temperature conditions combined with poor power supply which may affect drug efficacy, in addition to poor understanding of the physio-pharmacology of cancer pain management by health care providers [5]. Additionally, there is a lack of pharmacoeconomic studies assessing the net benefit of different formulation of rapidly acting opioid to assist decision-making by patients, clinicians, and payers to be cost-effective [6].

Limitations of the study

Our study limitations include the heterogeneity of the study population selected regarding the type of primary tumor site and the site of metastases as it is very difficult to have the total population with the same primary site. The relatively short follow-up period and this could be attributed to the short survival time of metastatic cancer patients and the possibility of lost them during follow-up period if the long-term follow-up period was prolonged, *in addition to the potential confounding role of the titration of the baseline analgesic in the results and the fact that these results are from a single center, which limits its generalizability.*

Conclusion

Our study demonstrated that oral piroxicam fast-dissolving tablet is an analgesic alternative to sublingual fentanyl in patients with bone metastasis to control *incident* BTP attacks with more favorable cost-benefit values. Both drugs reduced the VAS, duration of pain attacks, and number of rescue doses significantly. Sublingual fentanyl reduced the relation with others, sleep pattern and enjoyment of life parameter items of the BPI. *Finally, more research is needed to replicate these findings and confirm them before changing current medical practice.*

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Compliance with ethical standards

The study was approved by an Investigational Review Board of the Faculty of Medicine, Tanta University; an informed written consent was obtained from all patients participating in the study. This study was registered in the clinical trials registry (clinicaltrials.gov) with a unique identification number NCT02382653.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Margarit C, Juliá J, López R, Anton A, Escobar Y, Casas A, Cruz JJ, Galvez R, Mañas A, Zaragozá F (2012) Breakthrough cancer pain–still a challenge. J Pain Res 5:559–566
2. Mishra S, Bhatnagar S, Chaudhary P, Pratap S, Rana S (2009) Breakthrough cancer pain: review of prevalence, characteristics and management. Indian Journal of Palliative Care 15(1):14–18
3. Patel VF, Liu F, Brown MB (2011) Advances in oral transmucosal drug delivery. J Control Release 153:106–116
4. Lennernäs B, Frank-Lissbrant I, Lennernäs H, Kälkner KM, Derrick R, Howell J (2010) Sublingual administration of fentanyl to cancer patients is an effective treatment for breakthrough pain; results from a randomized phase II study. Palliat Med 24:286–293
5. Omoti AE, Omoti CE (2007) Pharmacological strategies for the management of cancer pain in developing countries. Pharm Pract 5(3):99–104
6. Kuo KL, Saokaew S, Stenehjem DD (2013) The pharmacoeconomics of breakthrough cancer pain. J Pain Palliat Care Pharmacother 27(2):167–175

7. Mercadante S, Radbruch L, Caraceni A, Cherny N, Kaasa S, Nauck F, Ripamonti C, De Conno F (2002) Episodic (breakthrough) pain consensus conference of an expert working group of the European Association for Palliative Care. Cancer 94:832–839
8. Mercadante S, Villari P, Ferrera P, Casuccio A (2004b) Optimization of opioid therapy for preventing incident pain associated with bone metastases. J Pain Symptom Manag 28:505–510
9. San K, Carla MB, Sheri LD, Jeff S, Tito RM, Charles SC (2004) Validity of the brief pain inventory for use in documenting the outcomes of patients with noncancer pain. Clin J Pain 20(5):309–318
10. Zhang H, Zhang J, Streisand JB (2002) Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications. Clin Pharmacokinet 41:661–680
11. Payne R (1997) Mechanisms and management of bone pain. Cancer Supplement 80(8):1608–1613
12. Yalcin S, Altundag K, Asil M, Tekuzman G (1998) Sublingual piroxicam for cancer pain. Med Oncol 15:137–139
13. G mez-Batiste X, Madrid F, Moreno F, Gracia A, Trelis J, Nabal M et al (2002) Breakthrough cancer pain: prevalence and characteristics in patients in Catalonia, Spain. J Pain Symptom Manag 24:45–52
14. Davies AN, Vriens J, Kennett A, McTaggart M (2008) An observational study of oncology patients' utilisation of breakthrough pain medication. J Pain Symptom Manag 35(4):406–411
15. Janecki M, Janecka J (2011) Breakthrough pain in patients with chronic cancer pain followed by palliative care and pain clinic physicians — an observational study. Palliat Med 10(1):29–34
16. Rauck RL, Tark M, Reyes E, Hayes TG, Bartkowiak AJ, Hassman D, Nalamachu S, Derrick R, Howell J (2009) Efficacy and long-term tolerability of sublingual fentanyl orally disintegrating tablet in the treatment of breakthrough cancer pain. Curr Med Res Opin 25(12):2877–2885
17. Smith HS (2013) Considerations in selecting rapid-onset opioids for the management of breakthrough pain. J Pain Res 6:189–200
18. Chwieduk CM, McKeage K (2010) Fentanyl sublingual: in breakthrough pain in opioid-tolerant adults with cancer. Drugs 70(17): 2281–2288
19. Überall MA, Müller-Schwefe GH (2011) Sublingual fentanyl orally disintegrating tablet in daily practice: efficacy, safety and tolerability in patients with breakthrough cancer pain. Curr Med Res Opin 27(7):1385–1394
20. Lister N, Warrington S, Boyce M, Eriksson C, Tamaoka M, Kilborn J (2011) Pharmacokinetics, safety, and tolerability of ascending doses of sublingual fentanyl, with and without naltrexone, in Japanese subjects. J Clin Pharmacol 51(8):1195–1204
21. Jandhyala R, Fullarton JR, Bennett MI (2013) Efficacy of rapid-onset oral fentanyl formulations vs. oral morphine for cancer-related breakthrough pain: a meta-analysis of comparative trials. J Pain Symptom Manag 12:1–8
22. Shimoyama N, Gomyo I, Teramoto O, Kojima K, Higuchi H, Yukitoshi N, Ohta E, Shimoyama M (2015) Efficacy and safety of sublingual fentanyl orally disintegrating tablet at doses determined from oral morphine rescue doses in the treatment of breakthrough cancer pain. Jpn J Clin Oncol 45(2):189–196
23. Davies AN, Dickman A, Reid C, Stevens AM, Zeppetella G (2009) The management of cancer-related breakthrough pain: recommendations of a task group of the Science Committee of the Association for Palliative Medicine of Great Britain and Ireland. Eur J Pain 13: 331–338