**Bulletin of Environment, Pharmacology and Life Sciences**
Bull. Env. Pharmacol. Life Sci., Spl Issue [2] 2023: 592-611.

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

**REVIEW ARTICLE** **OPEN ACCESS**

# Efficacy and Safety of Transmucosal Fentanyl Formulations for Breakthrough Cancer Pain: A Systematic Review and Meta-Analysis

**Jana Mhd Ghiath Ebrahim and Nurul Ain Mohd Tahir**
Faculty of Pharmacy, Universiti Kebangsaan Malaysia, Kuala Lumpur
*Corresponding Author
Mail: nurulainmt@ukm.edu.my
Email:janaibrahiim@outlook.com

**ABSTRACT**

*Breakthrough cancer pain (BTcP) refers to a brief episode of pain characterized by an intensity score exceeding 5 on the Numerical Rating Scale (NRS), typically lasting between 15 and 30 minutes, with a maximum duration of 60 minutes. It has a rapid onset, occurring within a few minutes. Transmucosal fentanyl formulations play a crucial role in treating BTcP due to their rapid onset of analgesic effect, short duration, and ease of administration through transmucosal routes. The aim is to assess the effectiveness and safety of transmucosal fentanyl formulations when administered orally or nasally specifically to manage breakthrough cancer pain (BTcP). A systematic literature review using electronic databases (PubMed, Web of Science, and Cochrane Library) from inception until April 2023. Only randomized clinical trials (RCTs) investigating the efficacy and safety of transmucosal fentanyl formulations for breakthrough cancer pain were selected. A meta-analysis was performed using RevMan software, with the primary outcome focusing on pain intensity difference (PID). Secondary outcomes included summed pain intensity difference (SPID) at 30 minutes after dosing, and safety measures such as adverse events (AEs) and overall AEs. 31 randomized controlled trials (RCTs) involving 2,467 patients were included. The meta-analysis demonstrated significant results favoring transmucosal fentanyl formulations for the primary outcome of pain intensity difference (PID) [SMD 0.42 [95% CI: 0.34 to 0.50 p < 0.00001]. Similarly, the analysis of the secondary outcome, the sum of pain intensity differences at 30 minutes (SPID), showed that transmucosal fentanyl formulations outperformed placebo/morphine [SMD: 1.70, 95% CI: 0.73 to 2.67, p = 0.0006]. Regarding safety, the overall analysis revealed no significant difference between transmucosal fentanyl formulations and morphine regarding adverse events (OR 0.90, 95% CI 0.53-1.53). Furthermore, the overall AEs showed similar incidences between transmucosal fentanyl formulations and morphine (OR 0.93, 95% CI 0.58-1.48).*
***Conclusions:*** *The systematic review and meta-analysis present compelling evidence that strongly supports the effectiveness and safety of transmucosal fentanyl formulations for the treatment of breakthrough cancer pain.*
***Keywords:*** *break through cancer pain, fentanyl, transmucosal fentanyl formulations*

Received 20 .10.2023 Revised 15.11.2023 Accepted 30 .12.2023

## INTRODUCTION

Breakthrough cancer pain (BTcP) refers to a brief episode of pain characterized by an intensity score exceeding 5 on the Numerical Rating Scale (NRS), typically lasting between 15 and 30 minutes, with a maximum duration of 60 minutes. The prevalence of BTCP ranges from 33% to 95% and varies in different studies (1).

Immediate-release morphine has been standard for transient cancer pain (2). but may not suit BTcP due to different characteristics (3). Fentanyl, a potent synthetic opioid, crosses the blood-brain barrier more rapidly than morphine, being up to 100 times more potent (2). Transmucosal fentanyl formulations play a crucial role in treating BTcP due to their rapid onset of analgesic effect, short duration, and ease of administration through transmucosal routes and demonstrated superior effectiveness compared to placebo or immediate-release opioids (4,5). Onset is typically ≤15 minutes ( 7). A previous narrative systematic review found transmucosal fentanyl formulations are effective and safe for BTcP management (8). As new evidence emerged, we conducted an updated systematic review with meta-analysis, assessing the effectiveness and safety of orally or nasally administered transmucosal fentanyl for BTcP management.

## MATERIAL AND METHOD

### Search strategy

The study selection process followed PRISMA guidelines (9). Ensuring comprehensive and transparent inclusion. Databases (PubMed, Web of Science, Cochrane Library) were searched from inception to April 2023 using (MeSH) terms: (Fentanyl) AND (cancer OR carcinoma OR neoplasm* OR tumor OR oncol*) AND (pain).

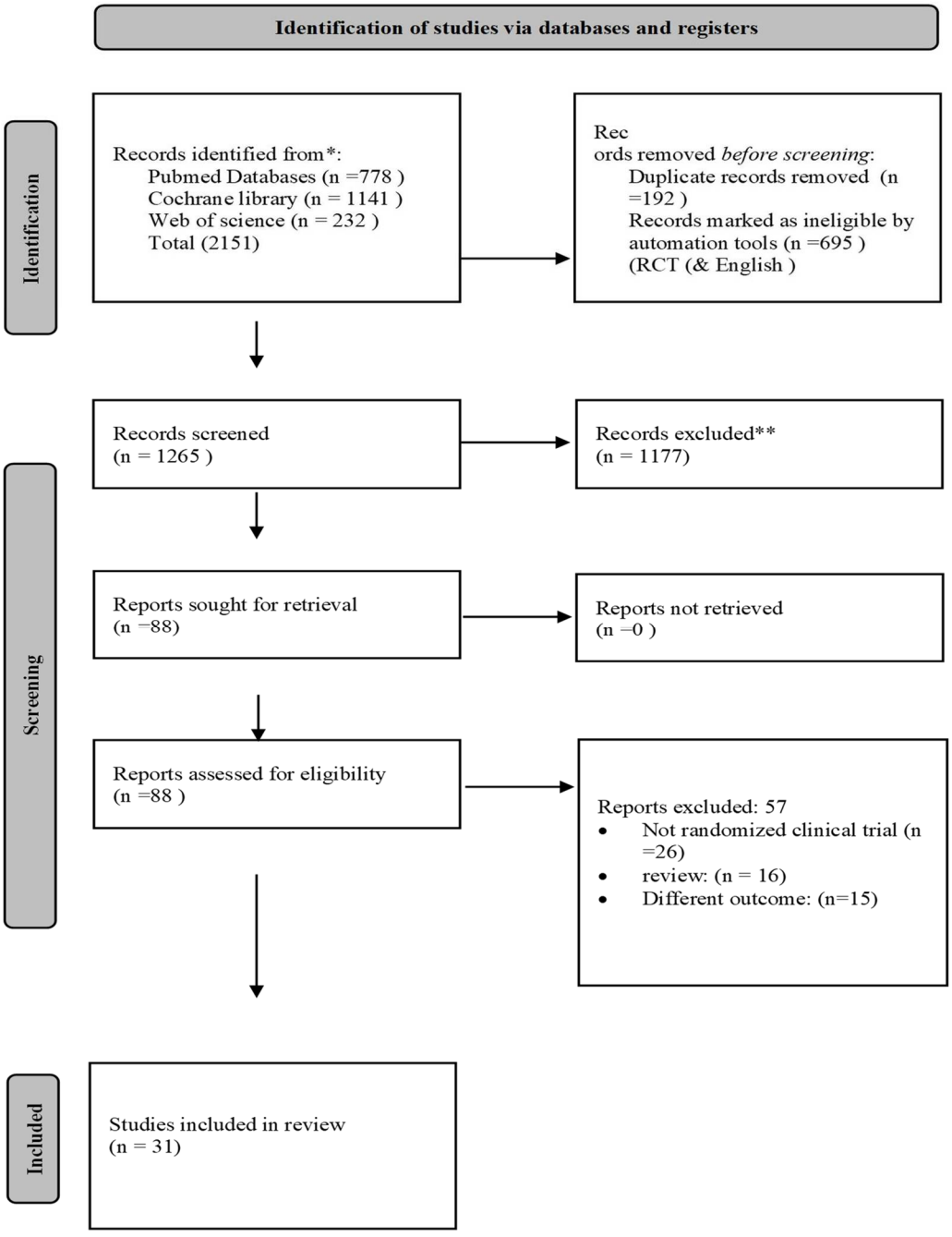


**Figure 3.1: A flowchart explaining the study inclusion process.**

### Selection procedure

In this systematic review, we focused on including only Randomized Clinical Trials (RCTs), the gold standard for evidence, as they offer high-quality and reliable data for evaluating the efficacy and safety of transmucosal fentanyl formulations. The RCTs needed to involve adult patients aged 18 and above, who had a confirmed diagnosis of cancer and experienced breakthrough pain episodes, treated with transmucosal fentanyl formulations administered orally or nasally and compared against a placebo or any other active medication. Furthermore, we limited our scope to articles that were published in English. Studies that exhibited incomplete or insufficient data for analysis and failed to provide the

necessary information for evaluating the research efficacy outcomes such as pain intensity reduction or relief, lacked safety outcome, were limited to abstracts only, had no full text available, or lacked a control arm, review articles were excluded from our analysis.

The efficacy outcome of the study focused on patient-reported pain and was assessed through the Pain Intensity Difference (PID) which is commonly derived by subtracting the baseline pain intensity, recorded before the intervention or treatment, from the pain intensity measured at a specified post-intervention time point. This parameter was identified as the primary efficacy outcome measure. The secondary efficacy outcome was evaluated using the Sum of Pain Intensity Difference (SPID) which involves summing the PID scores over a specific time interval. In terms of safety assessment, adverse events (AEs) associated with the use of fentanyl were analyzed. Additionally, the overall adverse events reported in the studies.

**Data extraction**

A tailored data collection form was used for meticulous data extraction. Two independent reviewers carefully extracted and discussed key details, such as author names, settings, study phases, population characteristics, sample size, intervention specifics, and primary outcome measures. These details were systematically organized in separate tables. Adverse events were also evaluated and included in separate tables to assess intervention safety.

**Data analysis**

Meta-analyses were conducted using Review Manager (RevMan, version 5.0) (10). Random effects models were consistently utilized. Mean differences (MD) with standard deviations (SD) and 95% confidence intervals (CI) were used for continuous outcomes. Dichotomous variables were reported as Odds Ratio (OR) with a corresponding 95% CI. Heterogeneity was assessed using the $I^2$ statistic 11).

The effectiveness of transmucosal fentanyl formulations was compared in meta-analyses, focusing on Pain Intensity Difference (PID) at 10, 15, and 30 mins. Summed Pain Intensity Difference (SPID) at 30 minutes after dosing was analyzed as a secondary outcome. Two meta-analyses evaluated safety outcomes, specifically comparing the incidence of adverse events (e.g., nausea, vomiting, somnolence) and overall adverse events reported in the studies.

## RESULTS

**Literature selection:**

A total of 2,151 records were initially identified **(Figure 3.1)**.192 duplicate records were removed, and automation tools excluded 695 records by restricting the PubMed search to RCTs and English articles.1,265 titles and abstracts of the articles were reviewed. Based on predefined criteria, 1,177 records were excluded. This resulted in 88 reports assessed for eligibility. Among them, 58 reports were excluded: 26 were not randomized clinical trials, 17 were review articles, and 15 had different outcomes. Ultimately, 31 studies met the inclusion criteria and were included in the review.

**Included studies:**

31 RCTs studied transmucosal fentanyl formulation: 15 compared it with a placebo, eight with morphine, and four explored different doses within the same formulation (11,12,13,14). Additionally, two studies compared intranasal fentanyl spray with various transmucosal fentanyl formulations (15,16) one study examined the comparison of intranasal fentanyl with intravenous hydromorphone (Banala et al. 2020), and another study compared fentanyl sublingual tablets with piroxicam (17).

**Study characteristics**

Studies were conducted in adult populations with a mean age ranging from 47-66 years. The total number of randomized patients was 2,467, with sample sizes ranging from 15 to 330 during the randomized treatment phase. Most studies were conducted in the United States (35.4%, n = 11/31), followed by Italy (19.7%, n = 6/31) and Europe (19.7%, n = 6/31) Patients experienced 1 to 4 breakthrough pain episodes per day, and background pain was managed using opioid medications such as oral morphine and transdermal fentanyl. Most studies followed a two-phase approach, comprising titration and treatment. The titration phase determined effective drug doses for pain relief and tolerable side effects, typically spanning from two to 21 days. Subsequently, the treatment phase involved multiple episodes or cycles of treatment, where the intervention's efficacy and safety were evaluated. Additionally, some studies incorporated follow-up phases to assess long-term safety, with the duration of these additional phases varying among the different studies **(Table 3.1).**

**Fentanyl buccal tablet (FBT)**

Six studies (697 participants) reported FBT effectiveness. Three studies compared FBT to placebo for BTcP treatment (18, 14, 7), and one study with oral morphine (19), Additionally, one study explored different FBT doses for optimal pain relief (12). Whereas, two different dosing strategies were compared in another study (13).

**Fentanyl Buccal Soluble Film (FBSF)**

One RCT compared FBSF to placebo with 80 patients (20).

**Fentanyl Sublingual Tablets (FSLT)**

Seven studies investigated FSLT for BTcP recruited a total of 525 participants were recruited. Overall, five with placebo (21, 22, 23, 24, 25) and one with subcutaneous morphine (SCM)(26), another study compared FSLT with oral piroxicam fast-dissolving tablets in patients with bone metastases 17).

**Fentanyl Sublingual Spray (FSS)**

Two studies compared FSS to placebo for the treatment of BTcP with a total of 124 recruited patients (27, 12).

**Oral Transmucosal Fentanyl Citrate (OTFC)**

Six studies reported the effectiveness of OTFC for BTcP with 473 recruited participants. One study compared OTFC with a placebo (31 ), and three studies with morphine (28, 29, 30).Additionally, two titration studies of different initial starting doses of OTFC 11, 32).

**Intranasal Fentanyl Spray (INFS)**

Five studies evaluated the effectiveness of INFS with a total number of 370 recruited participants. Among these studies, two were compared with placebo (33, 34), one with intravenous hydromorphone (IVH) (35), while two with other transmucosal fentanyl formulations (36, 37)**.**

**fentanyl Pectin Nasal Spray (FPNS)**

Four studies evaluated the effectiveness of FPNS with a total of 299 recruited participants. Among these studies, one compared with placebo (38), while in two studies it was compared to immediate-releasee morphine (39, 4)**,** and one with oral morphine (19).

**Efficacy assessment**

An overview of the efficacy outcome measures included in the research is summarized in **(Table 3.2)**. Three studies comparing FBT to placebo found that at 30 minutes, the pain intensity difference (PID30) ranged from 2.3 to 2.4, with a mean of 2.37. The mean difference in PID at 15 minutes was 1.2, while at 60 minutes, was 3.7. (18,20).

When comparing FBT to morphine, one study reported a difference in SPID30 (11). Additionally, another found that 75% of episodes achieved meaningful pain relief within 30 minutes (Kle15). Two dosing strategies, proportional (P) to daily dose and dose titration (T), resulted in a mean difference of 3.1 in PI (23). FBSF had mean PID at 15 and 30 minutes of 1.4 and 2.8, respectively, showing superiority over placebo.

FSLT also demonstrated superiority over placebo with a mean PID10 of 1.4 (range: 1.2-1.6) (23, 27,36). Compared to subcutaneous morphine (SCM), FSLT had a mean average pain intensity after 30 minutes of 5.0 (11). Similarly, no significant differences in VAS scores were found between FSLT and oral piroxicam fast-dissolving tablets (17).

FSS had a mean PID at 10, 15, and 30 minutes of 1.5, 2.1, and 2.8, respectively (Rauck et al. 2012), and one study reported that 64% of patients achieved the desired outcome (22).

OTFC showed that the mean PID30 was 2.4, while the mean PID15 was 1.6. (17). When compared to morphine, the mean PID30 was 4.0 (range: 2.9-4.6), and PID15 showed lower mean difference of 2.6. All studies demonstrated that fentanyl had superior efficacy to morphine**15,20)**, except one study that reported IV-MO had a shorter onset of analgesia(33). The mean PID15 was 2.35 when compared to the usual medication of patients (4)**,** and the mean pain relief scores at 15 and 30 min were 2.1 and 2.5, respectively (24).

INFS studies demonstrated a mean PID10 of 2.5 and superiority over placebo (27)**.** When compared to IVH, INFS showed lower pain change and quicker administration (04). INFS also showed significantly higher PID at 5 mins and SPID at 15 and 60 minutes compared to OTFC (12), However, there were no significant differences in pain intensity changes between INFS and FPNS (28)**.**

FPNS had a mean PID30 of 2.7. The PID at 10 and 15 minutes were lower, with mean differences of 1.3 and 2.0, respectively. Other parameters assessed included SPID30, FPNS had better efficacy than placebo in all these parameters (P). When compared to morphine, FPNS had a mean PID15 of 3.1, another parameter assesses was the pain intensity, pain relief, and SPID30. All parameters assessed showed superior efficacy to morphine (4, 11, 20).

**Primary efficacy outcome:**

**Meta-Analysis evaluating Pain Intensity Difference (PID)**

The meta-analysis of 17 trials (1255 patients) regarding the PID at 10, 15, and 30 minutes yielded significant results **(Figure 3.2)**. the analysis demonstrated that there is a significant difference in favor of Transmucosal Fentanyl formulations (TMF formulations) over placebo/morphine, with a standardized mean difference (SMD) of 0.42 [95% confidence interval (CI): 0.34 to 0.50], and overall effect Z-test of 10.01 ($p < 0.00001$). Heterogeneity was substantial ($p < 0.0001$; $I^2 = 54\%$).

In the subgroup analysis at 30 minutes, significant results favored transmucosal fentanyl over placebo, with SMD 0.61 [95% CI: 0.51 to 0.72] and an overall effect Z-test of 11.35 ($p < 0.00001$). However, there was no significant difference compared to morphine, with an SMD of 0.17 [95% CI: -0.09 to 0.44] and overall effect Z-test of 1.27 ($p = 0.20$). Similar findings were observed in further sub-analyses at 10 and 15 minutes, with SMDs of 0.44 [95% CI: 0.26 to 0.62] and 0.41 [95% CI: 0.28 to 0.54], respectively, favoring transmucosal fentanyl over placebo (both $p < 0.0001$). However, there was no significant difference compared to morphine at 15 minutes, with an SMD of 0.20 [95% CI: -0.05 to 0.45] and overall effect Z-test of 1.53 ($p = 0.13$).

**Secondary efficacy outcome:**

**Meta-Analysis evaluating the Summed Pain Intensity Difference (SPID30)**

The meta-analysis of 8 trials (1017 patients) comparing transmucosal fentanyl (TMF) formulations with placebo/oral morphine for SPID30 **(figure 3.3)**.The overall analysis, combining two subgroups, favored transmucosal fentanyl, SMD 1.70 [95% CI: 0.73 – 2.67], with high heterogeneity ($p < 0.00001$, $I^2 = 98\%$), and overall effect test Z= 3.43 ($p = 0.0006$).

For the first subgroup (TMF vs. placebo), a significant difference favored transmucosal fentanyl formulations over placebo, SMD 2.12 [95% CI: 0.83- 3.41], overall effect Z= 3.22 ($p = 0.001$). Similarly, the second subgroup (TMF vs. oral morphine) favored transmucosal fentanyl formulations, SMD 0.49 [95% CI: 0.05- 0.92], overall effect Z-value of 2.19 ($P = 0.03$).

**Safety assessment**

An overview of the safety outcome measures in **(Table 3.3).** Studies evaluating FBT vs. placebo reported opioid-related adverse events (AEs) like nausea, vomiting, and somnolence. A study noted two cases (N=2/123 2%) of oral mucosa ulcers related to FBT, leading to study withdrawal (27. One study reported that 10% of patients reported application site-related AEs (31). Compared to OM, both groups showed mild and similar adverse effects (17). In the FSLT vs. placebo trial, three patients had dry mouth, with two linked to the study drug (Gombert-Handoko 2014). Compared to SCM, one patient in FSLT group experienced moderate nausea, judged as possibly related to the study drug (11).

The safety of FSS was reported in two studies. One study found that peripheral edema and nausea were the most reported AEs, occurring in 9.4% of patients , In another study two patients (2.0%) had AEs likely related to the study drug (17). Regarding the OTFC formulation, dizziness (17%), nausea (14%), somnolence (8%), constipation (5%) were reported (20). Similarly, Somnolence, nausea, constipation, and dizziness were commonly reported (Coluzzi et al. 2001). Overall, the studies demonstrated that OTFC is safe and well-tolerable.

Furthermore, studies of INFS reported adverse effects including nausea, vertigo, and nasal discomfort (34, 35)**.** In one study, drowsiness and nausea were reported more in the INFS and FPNS groups, while nasal pruritis was similar between them. However, when FPNS was compared to placebo, less than ten patients reported nasal tolerability events (N=4/113 3.5%) of mild or moderate intensity (14). Moreover, when compared to morphine, vomiting, somnolence, dehydration, and nausea being the most common (18, 25, 7).

**Meta-analysis of safety outcome regarding the adverse events (nausea, vomiting, and somnolence)**

A meta-analysis of four studies compared transmucosal fentanyl formulations with oral morphine(4, 16, 46) included three subgroups: nausea, vomiting, and somnolence **(Figure 3.4)**.

The overall analysis found no significant difference in adverse event incidence between transmucosal fentanyl formulations and morphine, with an odds ratio of [OR 0.90; 95% CI 0.53-1.53], low heterogeneity ($p = 0.25$, $I^2 = 20\%$), and overall effect test Z= 0.38 ($p = 0.70$).

For the subgroup of nausea, showed no significant results, the odds ratio was [OR: 1.09, 95% CI: 0.25-4.8 $p = 0.91$]. The subgroup of vomiting showed similar results with an odds ratio of [OR 0.66, 95% CI 0.17-2.60 $p = 0.55$], and the subgroup of somnolence with an odds ratio of [OR 1.06, 95% CI 0.58-1.92 $p = 0.86$].

**Meta-analysis of safety outcome regarding the overall AEs.**

A meta-analysis of overall adverse events (AEs) in the previous studies. fentanyl group had 62 events out of 150 patients, and the morphine group had 76 events out of 206 patients **(Figure 3.5)**. The event rates for the Fentanyl and morphine groups were 41.3% and 36.9%, respectively. The analysis showed no significant difference between transmucosal fentanyl formulations and morphine, with an odds ratio of

[OR 0.93; 95% CI 0.58-1.48], and moderate heterogeneity (p = 0.13, $I^2$ = 46%). with an overall effect Z-score of 0.32 (p = 0.75).

**DISCUSSION**

Transmucosal fentanyl formulations have emerged as a viable option for the management of BTcP, offering rapid onset and convenient administration. Our systematic review, which encompassed 31 RCTs involving 2,467 patients, assessed the effectiveness of these formulations in managing BTcP. The evidence strongly supports the use of these formulations for this purpose. Meta-analysis of 17 RCTs consistently demonstrated their efficacy, reporting significant improvements in PID at 10, 15, and 30 minutes.

Transmucosal fentanyl formulations are a viable and effective option for managing BTcP. Patients treated with them experienced notable pain intensity reductions during breakthrough episodes. This finding is supported by SPID 30 minutes after dosing, consistently showing superior efficacy compared to placebo or oral morphine formulations in BTcP management.

The superior efficacy of transmucosal fentanyl formulations in managing breakthrough cancer pain (BTcP) can be attributed to their distinct pharmacokinetic profile. Immediate-release morphine reaches its peak analgesic activity approximately one hour after ingestion (41). In contrast, transmucosal fentanyl formulations offer a quicker onset of action by bypassing the gastrointestinal system. These formulations are rapidly absorbed through mucosal membranes, such as the oral cavity and nasal passages, leading to direct entry into the systemic circulation. This route of administration avoids first-pass metabolism and facilitates permeation across lipid-rich mucosal membranes, providing a faster onset of action (48). The efficient absorption and proximity to the target site contribute to the observed efficacy of transmucosal fentanyl formulations in managing BTcP, outperforming immediate-release morphine (42).

In alignment with the efficacy findings, the pharmacokinetic data of fentanyl products in our study further support these observations. For instance, orally-transmucosal fentanyl citrate (OTFC) reaches its maximum concentration (Tmax) within approximately 20 to 40 minutes, while fentanyl buccal tablet (FBT) takes around 47 minutes. Similarly, intranasal fentanyl has a Tmax of about 9 to 15 minutes, correlating with the rapid response observed in our study. These pharmacokinetic characteristics contribute to the prompt and effective pain relief demonstrated by transmucosal fentanyl formulations in the management of BTcP (43).

However, when compared to IV morphine, both medications were effective in managing BTcP (44), although IV morphine exhibited a shorter onset of action due to its immediate and direct delivery into the bloodstream. Nonetheless, transmucosal fentanyl formulations, such as OTFC, offer the advantage of easy discontinuation once sufficient analgesia is achieved.

These formulations showed good tolerance and manageable safety profiles, with consistent opioid-related adverse events and rare serious AEs. Our meta-analysis comparing these formulations to morphine found no significant difference in nausea, vomiting, and somnolence. Overall adverse events in both groups were similar. The comparable safety profile can be attributed to their shared pharmacological similarity as opioid analgesics, suggesting similar rates of adverse events. Transmucosal fentanyl formulations offer advantages as alternative treatment options for patients who struggle with traditional morphine formulations, adverse effects, or poor tolerance. They may improve tolerability and treatment adherence, especially for individuals with specific sensitivities to morphine.

Our findings align with prior research, confirming the efficacy of transmucosal fentanyl formulations. Earlier reviews concluded that these formulations are effective (45). Another systematic review indicated that fentanyl is superior to morphine in alleviating cancer pain (47).

Heterogeneity was observed among the included studies. It could be attributed to variations in study design, population characteristics, intervention protocols, different formulations and dosing regimens used, outcome measures, and assessment time points. Despite heterogeneity among studies, their effectiveness remains consistent. Considering these factors when interpreting the findings and their applicability to different populations and settings is important.

The systematic review has inherent limitations that should be acknowledged. These include differences in selection criteria, and population characteristics across studies. Moreover, the inclusion of only English-language studies introduces a potential language bias. These limitations can affect the generalizability of the findings of the review(48).

Despite limitations, our review's robust methodology and dependable data analysis enhance the credibility of the conclusions. Transmucosal fentanyl formulations provide swift pain relief, presenting a valuable option for cancer patients. Policymakers may take these findings into account when formulating guidelines, and future research should delve into long-term efficacy, safety, and cost-effectiveness aspects.

In conclusion, our systematic review and meta-analysis provide robust evidence endorsing the effectiveness and safety of transmucosal fentanyl formulations for managing BTcP. They offer a viable

option for rapid pain relief in cancer patients. Their safety profile is generally well-tolerated. Careful dosing strategy selection and patient monitoring are important for optimal pain control and minimizing adverse events.

**Table 3.1 Summary of the characteristics of studies comparing transmucosal fentanyl formulations for breakthrough cancer pain.**

| Study & Country | Type of fentanyl | Study phase | Sample size | Population | Intervention | Pain intensity at t=0 Mean ± SD (SE) | | Time points post-dose (mins) | Primary outcome |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Fentanyl | Control | | |
| Fentanyl vs placebo | | | | | | | | | |
| (Alberts et al. 2016) USA | FSS vs placebo | The screening period lasts up to 35 days. Open-label titration period lasting up to 26 days (100 µg to 1600 µg). Double-blind treatment period lasting up to 26 days | 32 | patients aged ≥18 years, with a mean age of 58.1 years, who were tolerant to opioids. Patients were treated with 60 mg of oral morphine, 30 mg of oxycodone, 8 mg of oral hydromorphone, or 25 mcg/hour of transdermal fentanyl. experienced 1-4 episodes per day of (BTcP). | For the treatment of ten episodes of BTcP, patients received seven doses of fentanyl sublingual spray and three doses of placebo in random order | NR | NR | NR | treatment satisfaction was assessed using the TSQM scale. |
| (Farrar et al. 1998) USA | OTFC vs placebo | -Titration phase (14 days), Treatment phase (10 episodes) | 86 | Adults mean age of 54 years experiencing persistent pain necessitating opioid therapy, either 60 mg of oral morphine or 50 µg of transdermal fentanyl. 1 BTcP episode/day treated with other opioids. | OTFC vs placebo in a ratio of 7:3. In case of ongoing pain, rescue medication or regular medication was provided. | 5.9 | 6.0 | 15, 30, 45, 60 | PID |
| (Gombert-Handoko 2014) Czech Republic | FE vs Placebo | Titration period Treatment phase | 73 | Adults mean age (64.7 years) with cancer. Pain is treated with 60 to 1000 mg of oral morphine daily or equivalent. Had 1 to 4 episodes of | FE vs placebo in a ratio of 6:3 rescue medication with usual treatment if pain relief is not achieved by 15-30 mins | 7.0±1.4 | 7.0±1.4 | 3, 6, 10, 15, 30, 60 | SPID30 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | BTcP per day | | | | | |
| (Hashemi et al. 2021)<br><br>Iran | FSLT vs placebo | Open-label titration phase treatment phase | 100 | Adults mean age of 47.0 years with cancer. treated with 60–1000 mg of oral morphine or equivalent opioid daily. have 1–4 episodes pain of pain | FSLT vs placebo and 60–600 mg of oral opioid regimen per day/30 mg of oral oxycodone daily | 8.09 | 8.43 | 15, 30. 45, 60 | SPID30 minutes after dosing |
| (Lennernas et al. 2010)<br><br>Sweden | FSLT vs placebo | Treatment phase Follow up phase | 38 | Adults mean age 63 years, have locally advanced metastatic cancer. Pain treated 30–1000 mg/day oral or morphine or 25–300 µg/h transdermal fentanyl. Had ≥4 BTcP episodes/day for 14 days | FSLT 100 µg vs 200 µg vs 400 µg vs Placebo in a ratio of 1:1:1:1, rescue medication with regular treatment if pain exists | NR | NR | 5, 10, 15, 20, 25 | PID |
| (Kosugi et al. 2014)<br><br>Japan | FBT vs Placebo | FBT dose titration phase Treatment phase (9 episodes) | 72 | Adults with a mean age of 61.2 years have cancer pain. managed with 30-1000 mg/day of oral morphine or equivalent opioids. | FBT vs placebo in a ratio of 6:3 rescue medication is used if the pain is not relieved after 30 mins | NR | NR | 15, 30, 60 | PID30 |
| (Kress et al. 2009)<br><br>Europe | INFS vs placebo | INFS titration phase (3 weeks), Treatment phase (8 episodes) | 110 | Adults with a median age of 61 inpatients or outpatients with chronic pain treated with opioid analgesic compounds, Had 3 BTcP episodes/week and a maximum of 4 | INFS vs. Placebo in a ratio of 3:1 in 2 consecutive sequences. Administering rescue medication 10 minutes after the second dose if pain still exists. | 6.4±1.4 | 6.4±1.3 | 10, 20, 40, 60 | PID10 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| (Portenoy et al. 2006)<br><br>USA | FBT vs Placebo | FBT dose titration phase, treatment phase (10 episodes) | 68 | Adults mean age 58 years with cancer pain. Treated with ≥60 mg/day morphine or 50–300 g/h transdermal fentanyl. had 1 to 4 BTcP episodes per day | FBT vs. Placebo in a ratio of 7:3. Rescue medication with regular treatment if pain exists. | 6.9± 0.2 | 6.9 ± 0.2 | 15. 30, 45, 60 | SPID30 |
| (Rauck et al. 2009)<br><br>USA | FSLT vs placebo | FSLT titration phase in 2-week Treatment phase (10 episodes) Follow-up phase to assess safety | 64 | Adults with a mean age of 53 have stable cancer-related pain. treated with 60–1000 mg/day oral morphine or 50–300µg/h transdermal fentanyl. Had 1 to 4 BTcP episodes/day. | FSLT vs. Placebo in a ratio of 7:3. 2-Hour interval between episodes. Rescue medication allowed | NR | NR | 10, 15, 30, 60 | SPID30 |
| (Rauck et al. 2010)<br><br>USA | FBSF vs placebo | Titration phase Treatment phase for 2 weeks Follow-up phase for 1 day | 80 | Adults with a mean age of 57 years had stable pain. Treated with 60–1000 mg/day oral morphine or 50–300µg/h transdermal fentanyl. Had 1 to 4 BTcP episodes/day. | FBSF vs. Placebo in a ratio of 6:3. The 4-hour interval between episodes. Rescue medication allowed | 6.9 ±0.2 | 6.9 ± 0.2 | 10,15,30,45,60 | SPID30 |
| (Rauck et al. 2012)<br><br>USA | FSS vs placebo | Titration phase Treatment phase 10-episode Follow-up phase | 92 | Adult with cancer Pain is managed with 5 mg immediate-release morphine or its equivalent. Experiencing 1-4 episodes of BTcP/day | FSS vs placebo in a ratio of 7:3. Usual medications are allowed if pain persists after 30 minutes | 63±20.1 | 62.5±20.5 | 5,10,15,30, 45, 60 | SPID30 |
| (Shimoyama et al. 2015)<br><br>Japan | FSLT vs placebo | Titration phase for max 21 days treatment phase (9 episodes of BTCP) for 21 days Extended treatment | 37 | Adult patients aged ≥20 years mean age 66.0 with cancer pain. treated with an opioid analgesic at fixed | FSLT vs placebo in a ratio of 6:3. Rescue medication with was used when additional doses were required | 68.31±17.68 | 68.31±17.68 | 15, 30, 60 | PID30 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | phase | | intervals at a stable daily dose for 7 days before the study, | | | | | |
| (Slatkin et al. 2007)<br><br>USA | FBT vs Placebo | Titration phase Treatment phase (10 episodes) | 75 | Adults with a mean age of 54 had pain managed with ≥25 g/h transdermal fentanyl. Had 1 to 4 BTcP episodes per day | FBT vs Placebo in a ratio of 7:3. rescue medication after 30 minutes | 6.4± 1.8 | 6.4 ±1.7 | 5, 10, 15, 30, 45, 60, 90, 120 | SPID60 |
| (Thronæs et al. 2015)<br><br>Europe | IFNS vs placebo | Titration phase Treatment phase Tolerability phase (12 weeks) | 15 | Adult cancer patients with BTcP episodes between 3 times per week and 4 times per day. pain treated with oral opioids or transdermal fentanyl morphine equivalent doses of 60-1000 mg/24 h | INFS 400µg (6 episodes) and placebo (2 episodes). rescue medications are allowed if insufficient pain relief | NR | NR | 5, 10, 30, 60 | PID10 |
| Fentanyl vs morphine | | | | | | | | | |
| (Bhatnagar et al. 2014)<br><br>India | OTFC vs oral morphine | treatment phase for 3 days | 186 | Adults with cancer and persistent moderate pain. treated with oral morphine 60 mg/day or equivalent. 1 to 4 episodes BTcP | OTFC 200µg vs oral morphine 10 mg tablets Rescue medication in both treatment groups if the pain was not adequately relieved. | 8.1±1.9 | 7.9±2.07 | 5, 15, 30, 60 | PID (5, 15, 30, and 60 minutes of drug administration) |
| (Coluzzi et al. 2001)<br><br>USA | OTFC vs IRMS | Titration phase (14 days) Treatment phase (10 episodes) | 75 | Adult means age 55 on Oral opioids, such as 60-1000 mg per day of morphine or 50-300 mg per hour of transdermal fentanyl. Had 1-4 BTcP episodes per day. | OTFC vs IRMS (5:5). rescue medication is advised if pain persists | 6.9 | 6.9 | 15, 30,45, 60 | PID on the VAS from 0 to 10 after 15 minutes. |
| (Davies et al. 2011) | FPNS vs IRMS | titration phase treatment | 84 | Cancer patients treated with | Oral treatment before nasal | NR | NR | 5, 10, 15,30.45,60 | Pain intensity (PI) and |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Europe and INDIA | | phase 10 BTCP episodes were treated | | opioid regimens such as 60 mg/day or more of oral morphine, Had 1-4 episodes of moderate-to-severe BTcP/day | spray for all episodes (5 with FPNS and oral placebo, 5 with IRMS and nasal spray placebo) | | | | pain relief scores |
| (Fallon et al. 2011)<br><br>Europe and INDIA | FPNS vs IRMS | titration phase treatment phase (10 BTcP episodes) | 79 | Patients with 1-4 episodes of BTcP/day treated with ≥ 60 mg/d oral morphine or equivalent | Oral treatment before nasal treatment for all episodes (5 with FPNS and oral placebo, 5 with IRMS and nasal spray placebo | NR | NR | 5, 10, 15,30.45,60 | PID15 |
| (Mercadante et al. 2007)<br><br>Italy | OTFC vs IV morphine | Treatment phase (2 episodes) | 25 | Adults with a median age of 59 with cancer pain Treated with a steady opioid regimen of greater than 60 mg oral morphine or 25 g transdermal fentanyl. | IV morphine (4-32 mg) vs OTFC (dose comparable to baseline scheme: 200-1600 g) (6 levels) (1:1), the 6-hour separation between episodes | 6.9±0.4 | 6.9±0.4 | 15,30 | \ SPID 30 |
| (Mercadante et al. 2015)<br>Italy | FBT vs OM | Treatment phase: two episodes of each study drug for three days | 72 | Adults with cancer pain on opioids ≥60 mg oral morphine equivalents per day 1-3 episodes of BTcP | FBT or OM in doses proportional to those used for background analgesia | 7.7 (1.1) | 7.7 (1.2) | 15, 30 | reduction in pain intensity by 33% and 50% at various time points after treatment with study drugs |
| (Mercadante et al. 2016)<br>Italy | FPNS vs OM | Treatment phase | 45 | Cancer patients mean age 63 with pain. Treated with ≥60 mg of OM equivalents/ day. Had ≥3 episodes of BTcP | FNPS or OM by administering. doses proportional to background opioid analgesia option to switch to the previous effective medication | 7.6 (0.6) | 7.6 (0.7) | 15, 30 | several patients benefit from study medications at different point intervals. |
| (Zecca et al. 2017)<br><br>Italy | FSLT + placebo vs SC morphine + placebo | Screening phase Randomization phase Follow up phase | 113 | Adults mean age 57.7 with severe cancer pain episode ≥ 6 on (NRS). | FSLT or SCM with a 1:1 allocation ratio. | 7.5±1.4 | 7.5±1.4 | 10, 20,30 | Average pain intensity (PI) at 10-, 20-, and 30-min |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Treated with 20 to 120 mg oral morphine equivalent daily dose | | | | | post administration |
| Fentanyl vs other interventions | | | | | | | | | |
| (Banala et al. 2020)<br><br>USA | INFS vs IVH | Treatment phase in ED | 82 | Patients with a mean of 52.9 years, had cancer pain. Treated with opioid therapy for 1 week or longer with 60 mg of oral morphine/day, and 25 mcg of transdermal fentanyl/hour. | 100 mcg of IN fentanyl vs IV hydromorphone 1.5 | NR | NR | 60 min | Pain relief change from treatment initiation (T0) to one hour later (T60) in an ED |
| (Christie et al. 1998)<br><br>USA | OTFC 200 vs 400 | Baseline phase, OTFC phase titrated to effective dose | 41 | Adult cancer patients with mean age: of 59 years had stable background pain and were using Fentanyl-TTS 50-300 µg/h for ATC medication | Randomized 200 µg or 400 µg OTFC | 6.8±1.6 | 6.8±1.9 | 0,15,30.60 | Pain intensity (PI)<br>Pain relief (PR)<br>Global satisfaction |
| (Kleeberg et al. 2015)<br><br>Multinational | FBT 100 or 200 | Screening phase 7 day<br>Randomized dose titration period (maximum of 7 days) treatment period (maximum of 8 days | 330 | Adults with a mean age of 59.8 years had cancer pain. Treated with ≥60 mg of oral morphine daily, ≥25 µg/h of transdermal fentanyl, or an equianalgesic dose of another opioid daily. Had 1-4 BTcP episodes per day | FBT 100 vs 200 µg with 4-hour intervals between episodes | 4.2 ±2.0 | NR | Nr | the proportion of patients who reach an effective dosage. |
| (Mercadante et al. 2009)<br><br>Europe | INFS vs OTFC | INFS titration phase<br>Treatment phase (6 episodes) | 101 | Adults with a mean age of 62 with chronic pain Treated with Opioid analgesic of 60-500 mg per day of morphine. Had 3-4 | INFS vs. OTFC in a ratio of 3:3. rescue drug allowed if pain persists | 6.4 ±1.4 | 6.4±1.5 | 5, 10, 15, 20, 30, 60 | PID10 |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | BTcP programs each week | | | | | |
| (Mercadante et al. 2012) Italy | FBT proportional vs FBT titration | Randomization phase: FBT in doses proportional to the daily opioid doses Treatment phase | 80 | Adults with a mean age of 61.3 years with cancer pain treated with strong opioids in doses of at least 60 mg of oral morphine equivalents had > 3 episodes of BTcP/day | FBT proportional vs dose titration | 7.6± 1 | 8.1±1.2 | 15 | Pain intensity difference at 15 mins |
| (Mercadante et al. 2014) Italy | INFS vs FPNS | Titration phase Treatment phase for 2 pairs of consecutive episodes. | 62 | Adults with a mean age of 63.4 years with cancer pain Treated with Opioids (≥60 mg oral morphine equivalents per day) 1 to 3 episodes of BTP per day. | INFS vs FPNS (doses proportional to background analgesia) | 6.8±0.98 | 6.8±0.83 | 20 mins | percentage of episodes with 33% or more reduction in pain intensity from baseline |
| (Portenoy et al. 1999) USA | OTFC 200 vs 400 mcg | Opioid dose stabilization, OTFC dose titration | 65 | Adult cancer patients with a mean age of 53, treated with oral opioid equivalent to 60-100mg oral morphine daily | 200 mcg or 400 mcg OTFC | NR | NR | 0,15,30.60 | PI, PR |
| (Yousef et al. 2019) Egypt | FSLT vs piroxicam | Titration phase over 2 weeks treatment phase | 100 | Adults with cancer pain (mean age 53.44) with bone metastases background pain treated according to WHO analgesic ladder. | FSLT 200 µg or 20 mg oral piroxicam fast-dissolving tablets 20 mg rescue dosage allowed if pain not changed. | 8.3±0.75 | 8.09±0.8 | NR | Reduction in VAS pain intensity from 0-10, in daily BTP attack frequency, and in time to reach maximum pain alleviation. |

ATC: around the clock, BTP: breakthrough pain, BTCP: breakthrough cancer pain, ED: emergency department, FBT: fentanyl buccal tablets, FBSF: fentanyl buccal soluble film, FE: Fentanyl Ethypharm, FSLT: Fentanyl sublingual tablets, FSLT: Fentanyl sublingual tablet, FPNS: fentanyl pectin nasal spray, FSS: fentanyl sublingual tablet, INFS: intranasal fentanyl spray, IRMS: immediate-release morphine sulfate, IVH: intravenous hydromorphone, NR: not reported, NRS: Numeric Rating Scale, OM: oral morphine, OTFC: oral transmucosal fentanyl citrate, PID: pain intensity difference, SPID: summed pain intensity difference, TSQM: Treatment Satisfaction Questionnaire for Medication, PI: pain intensity, PID: pain intensity difference, PR: pain relief.

**Table 3.2 An overview of the efficacy outcome measures comparing transmucosal fentanyl formulations for breakthrough cancer pain.**

| Study | Type of fentanyl | Summed pain intensity difference (SPID) | | | | Pain intensity reduction (PID) for fentanyl formulation and control | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 30 mins | | | | 10 mins | | | | 15 mins | | | | 30 mins | | | |
| | | Fentanyl | | Control | | Fentanyl | | Control | | Fentanyl | | Control | | Fentanyl | | Control | |
| | | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Fentanyl vs placebo | | | | | | | | | | | | | | | | | |
| (Farrar et al. 1998) | OTFC vs placebo | NR | NR | NR | NR | NR | NR | NR | NR | 1.6 | 1.2 | 1.0 | 1.1 | 2.4 | 1.4 | 1.5 | 1.3 |
| (Gombert-Handoko 2014) | FE vs placebo | 75.0 | 49.8 | 52.5 | 52.8 | 1.6 | 0.8 | 1.2 | 0.8 | 2.6 | 1.0 | 1.8 | 1.2 | 3.5 | 1.0 | 2.5 | 1.53 |
| (Kosugi et al. 2014) | FBT vs placebo | NR | NR | NR | NR | NR | NR | NR | NR | 1.2 | 1.2 | 1.1 | 1.0 | 2.4 | 1.0 | 2.0 | 1.0 |
| (Kress et al. 2009) | INFS vs placebo | NR | NR | NR | NR | 2.6 | 1.4 | 1.3 | 1.5 | NR | NR | NR | NR | NR | NR | NR | NR |
| (Portenoy et al. 2006) | FBT vs placebo | 3.0 | 1.5 | 1.8 | 1.5 | NR | NR | NR | NR | 0.9 | 1.1 | 0.5 | 0.9 | 2.3 | 1.5 | 1.4 | 1.3 |
| (Portenoy et al. 2010) | FPNS VS placebo | 6.6 | 5 | 4.4 | 5.5 | 1.3 | 1.3 | 0.9 | 1.3 | 2 | 1.5 | 1.3 | 1.5 | 2.7 | 1.6 | 1.6 | 1.9 |
| (Rauck et al. 2009) | FSLTVS placebo | 49.5 | 3.6 | 36.3 | 4.1 | 1.2 | 1.1 | 0.9 | 1.3 | 2 | 1.5 | 1.5 | 1.9 | 2.9 | 1.5 | 2.1 | 2.2 |
| (Rauck et al. 2010) | FBSF vs placebo | 47.9 | 3.9 | 38.1 | 4.3 | 0.8 | 0.6 | 0.7 | 0.7 | 1.4 | 0.8 | 1.2 | 0.9 | 2.5 | 1.0 | 1.9 | 1.3 |
| (Rauck et al. 2012) | FSS vs placebo | 640.3 | 47.8 | 399.6 | 40.8 | 1.5 | 1.3 | 1 | 0.9 | 2.1 | 1.3 | 1.3 | 1.3 | 2.8 | 1.5 | 1.6 | 1.3 |
| (Shimoyama et al. 2015) | FSLT VS placebo | NR | NR | NR | NR | NR | NR | NR | NR | 22.43 | 16.71 | 20.63 | 17.78 | 41.11 | 23.03 | 33.85 | 25.39 |
| (Slatkin et al. 2007) | FBT vs placebo | NR | NR | NR | NR | 0.9 | 0.8 | 0.5 | 0.8 | 1.4 | 1.2 | 0.8 | 1 | 2.4 | 1.6 | 1.3 | 1.3 |
| (Thronæs et al. 2015) | INFSVS placebo | | | | | 2.4 | 2.3 | 1.5 | 1.5 | | | | | | | | |
| fentanyl vs morphine | | | | | | | | | | | | | | | | | |
| (Bhatnagar et al. 2014) | OTFC vs oral morphine | NR | NR | NR | NR | NR | NR | NR | NR | 3 | 1.5 | 2.4 | 1.3 | 4.6 | 2 | 4.0 | 2 |
| (Coluzzi | OTFC | NR | NR | NR | NR | NR | N | NR | N | 1.9 | 1.7 | 1.5 | 1.4 | 2.9 | 1.7 | 2.4 | 1.3 |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| et al. 2001) | vs IRMS | | | | | | R | | R | | | | | | | | |
| (Fallon et al. 2011) | FPNS vs IRMS | NR | NR | NR | NR | 2.0 | 1.0 | 1.8 | 1.5 | 3.0 | 1.9 | 2.7 | 1.6 | 4.2 | 2 | 3.7 | 2.1 |
| (Mercadante et al. 2007) | OTFC vs IV morphine | NR | NR | NR | NR | NR | NR | NR | NR | 2.8 | 1.5 | 3.6 | 1.4 | 4.5 | 1.4 | 5.2 | 1.4 |
| (Mercadante et al. 2015) | FBT vs OM | 4.4 | 1.8 | 2.8 | 2.7 | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR | NR |
| (Mercadante et al. 2016) | FPNS vs OM | 4.87 | 1.7 | 4.5 | 1.5 | NR | NR | NR | NR | 3.24 | 1.7 | 2.7 | 1.2 | NR | NR | NR | NR |
| Head-to-head comparison of transmucosal fentanyl formulations | | | | | | | | | | | | | | | | | |
| (Mercadante et al. 2009) | INFS vs OTFC | NR | NR | NR | NR | 2.3 | 0.2 | 1.1 | 0.1 | 3.4 | 0.2 | 2 | 0.2 | 4.2 | 0.2 | 3.4 | 0.2 |
| (Mercadante et al. 2014) | INFS vs FPNS | NR | NR | NR | NR | 4.6 | 1.4 | 4.4 | 1.6 | NR | NR | NR | NR | NR | NR | NR | NR |

FBT: fentanyl buccal tablets, FBSF: fentanyl buccal soluble film, FE: Fentanyl Ethypharm, FSLT: Fentanyl sublingual tablets, FSLT: Fentanyl sublingual tablet, FPNS: fentanyl pectin nasal spray, FSS; fentanyl sublingual tablet, INFS: intranasal fentanyl spray, IRMS: immediate-release morphine sulfate, NR: not reported, OM: oral morphine, OTFC: oral transmucosal fentanyl citrate, PID: pain intensity difference, SD: standard deviation.

**Table 3.3 An overview of the safety outcome measures comparing transmucosal fentanyl formulations with morphine for breakthrough cancer pain.**

| Study | Competitor | Number of patients experiencing adverse events in the study (N) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Nausea | | Vomiting | | Somnolence | | AE overall | |
| | | Fentanyl | Control | Fentanyl | Control | Fentanyl | Control | | |
| (Alberts et al. 2016) | FSS vs placebo | 3 | | 2 | | 2 | | NR | |
| (Coluzzi et al. 2001) | OTFC vs Immediate release morphine | 18 | | NR | | NR | | 62 | |
| (Fallon et al. 2011) | OTFC VS IRMO | 1 | 1 | 2 | 3 | 4 | 1 | 15 | 13 |
| (Farrar et al. 1998) | OTFC vs placebo | 18 | | 14 | | 11 | | 77 | |
| (Gombert-Handoko 2014) | FE vs placebo | 4.4%* | | 5.5%* | | NR | | NR | |
| (Hashemi et al. 2021) | FSLT vs placebo | NR | | NR | | 6 | | NR | |
| (Kleeberg et al. 2015) | FBT 100 vs FBT 200 | 5 | 5 | 3 | NR | 5 | 4 | NR | |
| (Kosugi et al. 2014) | FBT vs placebo | 11 | | 14 | | 28 | | NR | |
| (Mercadante et al. 2009) | INFS vs OTFC | 10 | 9 | 6 | 4 | 2 | 3 | 56 | 41 |
| (Mercadante et al. 2014) | INFS vs FPNS | | | | | 3 | 2 | NR | |
| (Mercadante et al. 2007) | OTFC vs IV-MO | 4 | 2 | NR | NR | 7 | 10 | 12 | 15 |
| (Mercadante et al. 2016) | FPNS vs oral morphine | 4 | 10 | 4 | 10 | 17 | 15 | 27 | 32 |
| (Portenoy 1999) | OTFC 200 vs 400 mcg | 5%* | | NR | | NR | | NR | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| (Portenoy et al. 2006) | FBT vs placebo | 27 | | 13 | | 12 | | 107%* | NR |
| (Portenoy et al. 2010) | FPNS VS placebo | 10 | | 12 | | 4 | | 58 | 4 |
| (Rauck et al. 2009) | FSLT VS placebo | 16 | | 7 | | NR | | 37 | NR |
| (Rauck et al. 2010) | FBSF vs placebo | 8 | | 6 | | 9 | | 56 | NR |
| Rauck et al. 2012) | FSS vs placebo | 7 | | 4 | | 2 | | 2 | NR |
| (Shimoyama et al. 2015) | FSLT vs placebo | 3 | | 3 | | 4 | | 42 | NR |
| (Thronæs et al. 2015) | INFS VS placebo | 10 | | 3 | | 1 | | 146 | NR |
| (Zecca et al. 2017) | FSLT vs SCM | 0 | 1 | 0 | 1 | 6 | 5 | 15 | 16 |

FBT: fentanyl buccal tablets, FBSF: fentanyl buccal soluble film, FE: Fentanyl Ethypharm, FSLT: Fentanyl sublingual tablets, FSLT: Fentanyl sublingual tablet, FPNS: fentanyl pectin nasal spray, FSS; fentanyl sublingual tablet, INFS: intranasal fentanyl spray, IMRS: immediate-release morphine sulfate, NR: not reported, OM: oral morphine, OTFC: oral transmucosal fentanyl citrate.
*The percentages were based on the number of adverse events per total number of patients in the specified groups.

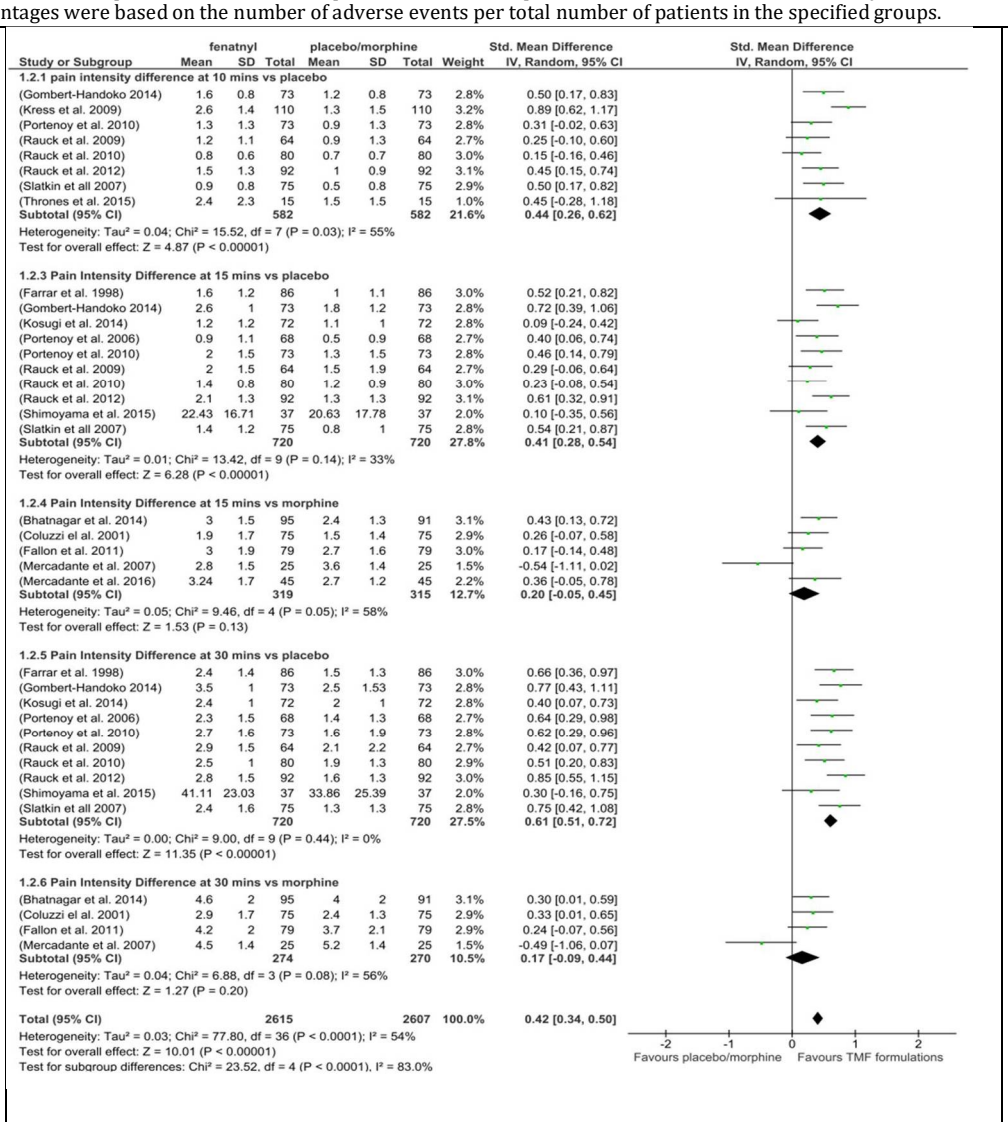


**Figure 3.2 Forest plot regarding the Pain Intensity Difference (PID) for breakthrough cancer pain.**

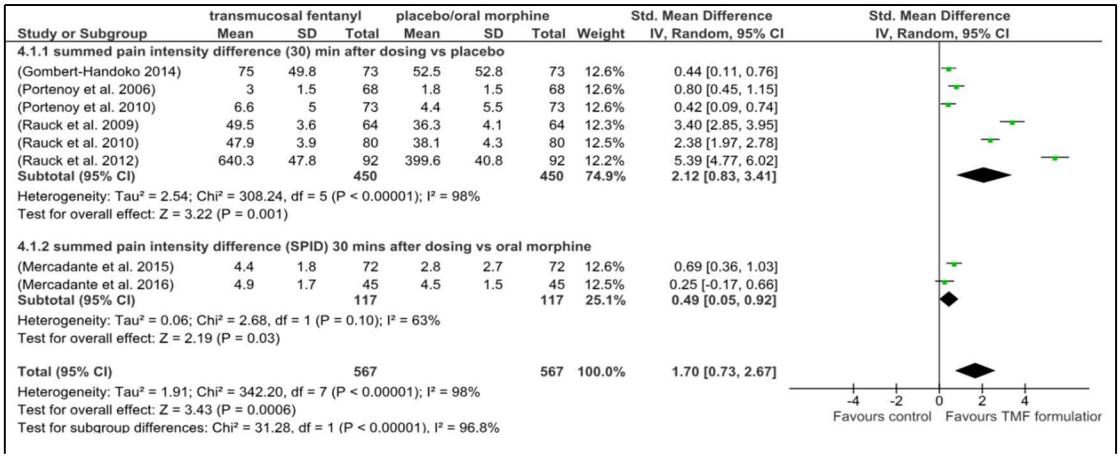


**Figure 3.3 Forest plot regarding the Summed Pain Intensity Difference at 30 minutes (SPID30) after dosing for breakthrough cancer pain**

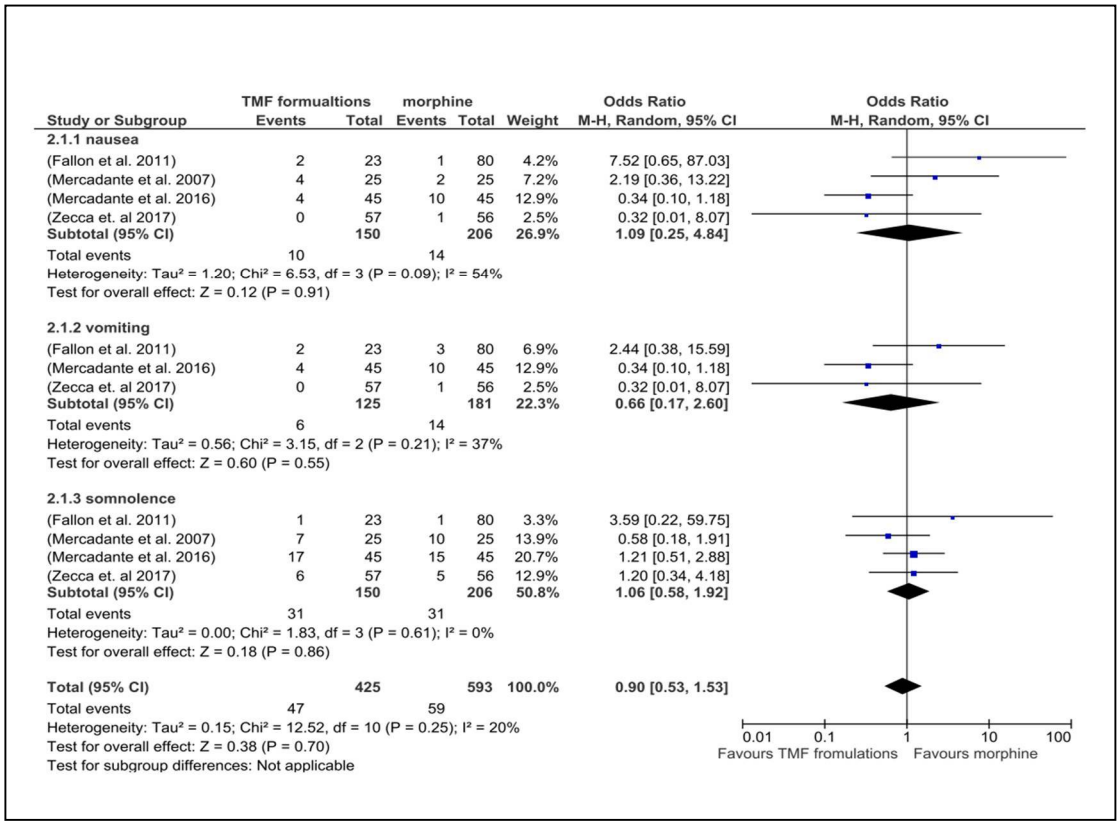


**Figure 3.4 Forest plot regarding the adverse events of transmucosal fentanyl formulations compared to morphine for breakthrough cancer pain.**

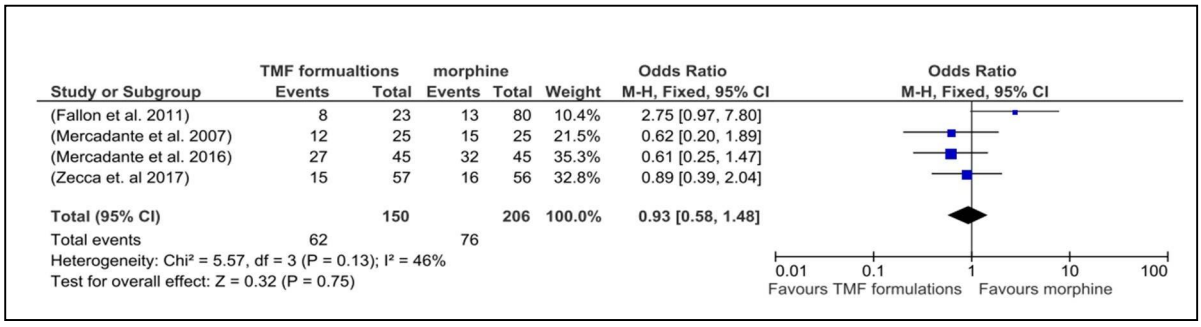


**Figure 3.5 Forest plot regarding the adverse events of transmucosal fentanyl formulations compared to morphine for breakthrough cancer pain.**

**ACKNOWLEDGEMENTS**

I want to take this opportunity to express my sincere gratitude to all those who have played a part, directly or indirectly, in the successful completion of my thesis. A special mention goes to my supervisor, Dr. Nurul Ain Mohd Tahir, whose unwavering guidance and trust have been instrumental in carrying out my research with confidence and focus. Her positive feedback and constructive suggestions have motivated me to overcome various challenges.

I also extend my thanks to all my lecturers for their constant encouragement and support, which has served as a driving force in achieving the set objectives. Moreover, I am deeply grateful to my beloved parents and sister for their unwavering love, emotional guidance, and spiritual support throughout this journey. Their continuous encouragement, patience, and belief in my abilities have been a constant source of motivation, propelling me through successes and setbacks. Without their courage and determination, I would not have been able to navigate the obstacles encountered during the completion of my thesis.

**REFERENCES**

1. Løhre, E. T., Thronæs, M., Brunelli, C., Kaasa, S. & Klepstad, P. (2020). An in-hospital clinical care pathway with integrated decision support for cancer pain management reduced pain intensity and needs for a hospital stay. Support Care Cancer 28(2): 671-682.
2. Fallon, M., Giusti, R., Aielli, F., Hoskin, P., Rolke, R., Sharma, M. & Ripamonti, C. I. (2018). Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. Ann Oncol 29(Suppl 4): iv166-iv191.
3. 3 Mercadante, S., Marchetti, P., Cuomo, A., Caraceni, A., Mediati, R. D., Vellucci, R., Mammucari, M., Natoli, S., Lazzari, M., Dauri, M., Adile, C., Airoldi, M., Azzarello, G., Bandera, M., Blasi, L., Cartenì, G., Chiurazzi, B., Costanzo, B. V. P., Degiovanni, D., Fusco, F., Guardamagna, V., Iaffaioli, V., Liguori, S., Palermo, L., Mameli, S., Masedu, F., Mattioli, R., Mazzei, T., Melotti, R. M., Menardo, V., Miotti, D., Moroso, S., Pascoletti, G., De Santis, S., Orsetti, R., Papa, A., Ricci, S., Scelzi, E., Sofia, M., Tonini, G., Valle, A. & Aielli, F. (2018). Factors Influencing the Clinical Presentation of Breakthrough Pain in Cancer Patients. Cancers (Basel) 10(6): 123-127
4. Fallon, M., Reale, C., Davies, A., Lux, A. E., Kumar, K., Stachowiak, A. & Galvez, R. (2011). Efficacy and safety of fentanyl pectin nasal spray compared with immediate-release morphine sulfate tablets in the treatment of breakthrough cancer pain: a multicenter, randomized, controlled, double-blind, double-dummy multiple-crossover study. J Support Oncol 9(6): 224-231.
5. Rauck, R., Reynolds, L., Geach, J., Bull, J., Stearns, L., Scherlis, M., Parikh, N. & Dillaha, L. (2012). Efficacy and safety of fentanyl sublingual spray for the treatment of breakthrough cancer pain: a randomized, double-blind, placebo-controlled study. Current Medical Research and Opinion 28(5): 859-870.
6. Christie, J. M., Simmonds, M., Patt, R., Coluzzi, P., Busch, M. A., Nordbrock, E. & Portenoy, R. K. (1998). Dose-titration, multicenter study of oral transmucosal fentanyl citrate for the treatment of breakthrough pain in cancer patients using transdermal fentanyl for persistent pain. Journal of Clinical Oncology 16(10): 3238-3245.
7. Slatkin, N. E., Xie, F., Messina, J. & Segal, T. J. (2007). Fentanyl buccal tablet for relief of breakthrough pain in opioid-tolerant patients with cancer-related chronic pain. Journal of supportive oncology 5(7): 327-334.
8. Rogríguez, D., Urrutia, G., Escobar, Y., Moya, J. & Murillo, M. (2015). Efficacy and Safety of Oral or Nasal Fentanyl for Treatment of Breakthrough Pain in Cancer Patients: A Systematic Review. J Pain Palliat Care Pharmacother 29(3): 228-246.
9. Page, M. J., Mckenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., Mcdonald, S., Mcguinness, L. A., Stewart, L. A., Thomas, J., Tricco, A. C., Welch, V. A., Whiting, P. & Moher, D. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Systematic Reviews 10(1): 89.
10. Revman, R. M. (2008). Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008. version 5.
11. Higgins, J. P., Thompson, S. G., Deeks, J. J. & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. Bmj 327(7414): 557-560.
12. Kleeberg, U. R., Davies, A., Jarosz, J., Mercadante, S., Poulain, P., O'brien, T., Schneid, H. & Kress, H. G. (2015). Pan-European, open-label dose titration study of fentanyl buccal tablet in patients with breakthrough cancer pain. Eur J Pain 19(4): 528-537.
13. Mercadante, S., Gatti, A., Porzio, G., Lo Presti, C., Aielli, F., Adile, C. & Casuccio, A. (2012). Dosing fentanyl buccal tablet for breakthrough cancer pain: dose titration versus proportional doses. Curr Med Res Opin 28(6): 963-968.
14. Portenoy, R. K., Taylor, D., Messina, J. & Tremmel, L. (2006). A randomized, placebo-controlled study of fentanyl buccal tablet for breakthrough pain in opioid-treated patients with cancer. Clin J Pain 22(9): 805-811.

15. Mercadante, S., Prestia, G., Adile, C. & Casuccio, A. (2014). Intranasal fentanyl versus fentanyl pectin nasal spray for the management of breakthrough cancer pain in doses proportional to basal opioid regimen. J Pain 15(6): 602-607.
16. Mercadante, S., Radbruch, L., Davies, A., Poulain, P., Sitte, T., Perkins, P., Colberg, T. & Camba, M. A. (2009). A comparison of intranasal fentanyl spray with oral transmucosal fentanyl citrate for the treatment of breakthrough cancer pain: an open-label, randomised, crossover trial. Current medical research and opinion 25(11): 2805-2815.
17. Yousef, A. A. & Alzeftawy, A. E. (2019). The efficacy of oral piroxicam fast-dissolving tablets versus sublingual fentanyl in incident breakthrough pain due to bone metastases: a double-blinded randomized study. Supportive care in cancer 27(6): 2171-2177.
18. Kosugi, T., Hamada, S., Takigawa, C., Shinozaki, K., Kunikane, H., Goto, F., Tanda, S., Shima, Y., Yomiya, K., Matoba, M., Adachi, I., Yoshimoto, T. & Eguchi, K. (2014). A randomized, double-blind, placebo-controlled study of fentanyl buccal tablets for breakthrough pain: efficacy and safety in Japanese cancer patients. J Pain Symptom Manage 47(6): 990-1000.
19. Mercadante, S., Adile, C., Cuomo, A., Aielli, F., Cortegiani, A., Casuccio, A. & Porzio, G. (2015). Fentanyl Buccal Tablet vs. Oral Morphine in Doses Proportional to the Basal Opioid Regimen for the Management of Breakthrough Cancer Pain: A Randomized, Crossover, Comparison Study. J Pain Symptom Manage 50(5): 579-586.
20. Rauck, R., North, J., Gever, L. N., Tagarro, I. & Finn, A. L. (2010). Fentanyl buccal soluble film (FBSF) for breakthrough pain in patients with cancer: a randomized, double-blind, placebo-controlled study. Ann Oncol 21(6): 1308-1314.
21. Gombert-Handoko, K. B. (2014). A randomized, placebo-controlled study of a new sublingual formulation of fentanyl citrate (fentanyl ethypharm) for breakthrough pain in opioid-treated patients with cancer. Clinical Therapeutics 36(11): 1704.
22. Hashemi, M., Zali, A., Golmakani, E., Delshad, M. H., Shadnoush, M. & Akbari, M. E. (2021). Efficacy, safety, and tolerability of sublingual fentanyl orally disintegrating tablet in the treatment of breakthrough cancer pain: a randomized, double-blind, placebo-controlled study. Daru-Journal of Pharmaceutical Sciences 29(1): 51-59.
23. Lennernas, B., Frank-Lissbrant, I., Lennernas, H., Kalkner, K. M., 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. Palliative Medicine 24(3): 286-293.
24. Rauck, R. L., Tark, M., Reyes, E., Hayes, T. G., Bartkowiak, A. J., 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. Current Medical Research and Opinion 25(12): 2877-2885.
25. 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. Japanese Journal of Clinical Oncology 45(2): 189-196.
26. Zecca, E., Brunelli, C., Centurioni, F., Manzoni, A., Pigni, A. & Caraceni, A. (2017). Fentanyl Sublingual Tablets Versus Subcutaneous Morphine for the Management of Severe Cancer Pain Episodes in Patients Receiving Opioid Treatment: A Double-Blind, Randomized, Noninferiority Trial. Journal of Clinical Oncology 35(7): 759-765.
27. Alberts, D. S., Smith, C. C., Parikh, N. & Rauck, R. L. (2016). Fentanyl sublingual spray for breakthrough cancer pain in patients receiving transdermal fentanyl. Pain Management 6(5): 427-434.
28. Bhatnagar, S., Devi, S., Vinod, N. K., Jain, P. N., Durgaprasad, G., Maroo, S. H. & Patel, K. R. (2014). Safety and Efficacy of Oral Transmucosal Fentanyl Citrate Compared to Morphine Sulphate Immediate Release Tablet in Management of Breakthrough Cancer Pain. Indian Journal of Palliative Care 20(3): 182-187.
29. Coluzzi, P. H., Schwartzberg, L., Conroy, J. D., Charapata, S., Gay, M., Busch, M. A., Chavez, J., Ashley, J., Lebo, D., Mccracken, M. & Portenoy, R. K. (2001). Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC) and morphine sulfate immediate release (MSIR). Pain 91(1-2): 123-130.
30. Mercadante, S., Villari, P., Ferrera, P., Casuccio, A., Mangione, S. & Intravaia, G. (2007). Transmucosal fentanyl vs intravenous morphine in doses proportional to basal opioid regimen for episodic-breakthrough pain. British journal of cancer 96(12): 1828-1833.
31. Farrar, J. T., Cleary, J., Rauck, R., Busch, M. & Nordbrock, E. (1998). Oral transmucosal fentanyl citrate: randomized, double-blinded, placebo-controlled trial for the treatment of breakthrough pain in cancer patients. J Natl Cancer Inst 90(8): 611-616.
32. Portenoy. (1999). Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. Pain 79(2-3): 303-312.
33. Kress, H. G., Orońska, A., Kaczmarek, Z., Kaasa, S., Colberg, T. & Nolte, T. (2009). Efficacy and tolerability of intranasal fentanyl spray 50 to 200 microg for breakthrough pain in patients with cancer: a phase III, multinational, randomized, double-blind, placebo-controlled, crossover trial with a 10-month, open-label extension treatment period. Clin Ther 31(6): 1177-1191.
34. Thronæs, M., Popper, L., Eeg, M., Jaatun, E., Kvitberg, M. & Kaasa, S. (2015). Efficacy and tolerability of intranasal fentanyl spray in cancer patients with breakthrough pain. Clin 17 Ther 37(3): 585-596.
35. Banala, S. R., Khattab, O. K., Page, V. D., Warneke, C. L., Todd, K. H. & Yeung, S. C. J. (2020). Intranasal fentanyl spray versus intravenous opioids for the treatment of severe pain in patients with cancer in the emergency department setting: A randomized controlled trial. Plos One 15(7):
36. Mercadante, S., Adile, C., Cuomo, A., Aielli, F., Cortegiani, A., Casuccio, A. & Porzio, G. (2015). Fentanyl Buccal Tablet vs. Oral Morphine in Doses Proportional to the Basal Opioid Regimen for the Management of

Breakthrough Cancer Pain: a Randomized, Crossover, Comparison Study. Journal of pain and symptom management 50(5): 579-586.
37. Mercadante, S., Aielli, F., Adile, C., Costanzi, A. & Casuccio, A. (2016). Fentanyl Pectin Nasal Spray Versus Oral Morphine in Doses Proportional to the Basal Opioid Regimen for the Management of Breakthrough Cancer Pain: A Comparative Study. Journal of Pain and Symptom Management 52(1): 27-34.
38. Portenoy, R. K., Burton, A. W., Gabrail, N. & Taylor, D. (2010). A multicenter, placebo-controlled, double-blind, multiple-crossover study of Fentanyl Pectin Nasal Spray (FPNS) in the treatment of breakthrough cancer pain. Pain 151(3): 617-624.
39. Davies, A., Sitte, T., Elsner, F., Reale, C., Espinosa, J., Brooks, D. & Fallon, M. (2011). Consistency of Efficacy, Patient Acceptability, and Nasal Tolerability of Fentanyl Pectin Nasal Spray Compared with Immediate-Release Morphine Sulfate in Breakthrough Cancer Pain. Journal of Pain and Symptom Management 41(2): 358-366.
40. Manirakiza, A., Irakoze, L., Manirakiza, S. & Bizimana, P. (2020). Efficacy and Safety of Fentanyl Compared With Morphine among Adult Patients with Cancer: A Meta-Analysis. East Afr Health Res J 4(1): 8-16.
41. Banala, S. R., Khattab, O. K., Page, V. D., Warneke, C. L., Todd, K. H. & Yeung, S. J. (2020). Intranasal fentanyl spray versus intravenous opioids for the treatment of severe pain in patients with cancer in the emergency department setting: A randomized controlled trial. PLoS One 15(7): e0235461.
42. Lennernäs, B., Frank-Lissbrant, I., Lennernäs, H., Kälkner, K. M., 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(3): 286-293.
43. Maindet, C., Burnod, A., Minello, C., George, B., Allano, G. & Lemaire, A. (2019). Strategies of complementary and integrative therapies in cancer-related pain-attaining exhaustive cancer pain management. Support Care Cancer 27(8): 3119-3132.
44. Portenoy, R. K., Payne, R., Coluzzi, P., Raschko, J. W., Lyss, A., Busch, M. A., Frigerio, V., Ingham, J., Loseth, D. B., Nordbrock, E. & Et Al. (1999). Oral transmucosal fentanyl citrate (OTFC) for the treatment of breakthrough pain in cancer patients: a controlled dose titration study. Pain 79(2-3): 303-312.
45. Rauck, R., Reynolds, L., Geach, J., Bull, J., Stearns, L., Scherlis, M., Parikh, N. & Dillaha, L. (2012). Efficacy and safety of fentanyl sublingual spray for the treatment of breakthrough cancer pain: a randomized, double-blind, placebo-controlled study. Curr Med Res Opin 28(5): 859-870.
46. Zecca, E., Brunelli, C., Centurioni, F., Manzoni, A., Pigni, A. & Caraceni, A. (2017). Fentanyl Sublingual Tablets Versus Subcutaneous Morphine for the Management of Severe Cancer Pain Episodes in Patients Receiving Opioid Treatment: A Double-Blind, Randomized, Noninferiority Trial. J Clin Oncol 35(7): 759-765.
47. Brząkała, J. & Leppert, W. (2019). The role of rapid onset fentanyl products in the management of breakthrough pain in cancer patients. Pharmacol Rep 71(3): 438-442.
48. Moore, N., Darwish, M., Amores, X. & Schneid, H. (2012). A review of the pharmacokinetic profile of transmucosal fentanyl formulations. Current medical research and opinion 28(11): 1781-1790.

**CITATION OF THIS ARTICLE**

Jana Mhd Ghiath Ebrahim, and Nurul Ain Mohd Tahir. Efficacy and Safety of Transmucosal Fentanyl Formulations for Breakthrough Cancer Pain: A Systematic Review and Meta-Analysis. Bull. Env. Pharmacol. Life Sci., Spl Issue [2]: 2023: 592-611.