# A Preliminary Study of Prophylactic Fentanyl Pectin Nasal Spray (FPNS) for Exercise-Induced Breakthrough Dyspnea

**Principal investigator:** Dr. David Hui
**Supportive Care Co-investigators:** Dr. Eduardo Bruera, Dr. Suresh Reddy, Dr. Anne Tsao
**Biostatistics Co-investigator:** Mr. Gary Chisholm

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## A. Study Objectives

**Primary objective**

To determine the effect of prophylactic fentanyl pectin nasal spray (FPNS) on the **intensity of exercise-induced breakthrough dyspnea** (numeric rating scale, adjusted for distance walked) between the **first** and **second** 6 minute walk tests. We aim to determine the effect size for both FPNS and placebo arm to inform a larger, adequately powered confirmatory randomized controlled trial.

**Secondary objectives**

1. To determine the effect of prophylactic FPNS on the **walk distance, neurocognitive function, and adverse effects** between the **first** and **second** 6 minute walk tests.

2. To determine the effect of prophylactic FPNS on the **intensity of dyspnea, walk distance, neurocognitive function, and adverse effects** between the **first** and **third** 6 minute walk tests.

3. To compare prophylactic FPNS and placebo on their ability to reduce the intensity of **exercise-induced breakthrough dyspnea, walk distance, neurocognitive function, and adverse effects** between the **first** and **second** 6 minute walk tests, and also between the **first** and **third** 6 minute walk tests.

## B. Background

**B.1. Significance of Dyspnea.** Dyspnea is a subjective awareness of difficulty breathing, which may be associated with the distressing sensation of suffocation. It is one of the most common and most feared symptoms among cancer patients, occurring in up to 70% of patients in the last 6 weeks of life (Ben-Aharon et al. 2008). Dyspnea is associated with fatigue, anxiety, decreased function and quality of life, and increased mortality (Hauser et al. 2006, Maltoni et al. 2005).

In a study examining 70 patients with dyspnea, 43 (61%) reported breakthrough (episodic or incidental) dyspnea only, 13 (19%) had constant dyspnea only, and 14 (20%) experienced both constant and breakthrough dyspnea. A substantial proportion of the patients with breakthrough dyspnea (18/57, 32%) presented with 5 or more episodes per day, and the majority of episodes lasted <10 minutes (Reddy *et al.* 2009). Breakthrough dyspnea is particularly challenging to treat because of its transient and episodic nature.

Exercise-induced dyspnea (or shortness of breath on exertion) is a subtype of breakthrough dyspnea. This is similar to incident pain (on ambulation) which is a subtype of breakthrough pain. Breakthrough dyspnea has 4 major triggers: exertion, emotional changes, the environment (e.g. altitude, smog), and spontaneous/idiopathic. Because many cancer patients experience severe shortness of breath with activities (i.e. walking), they have to limit their function significantly. In a recent study conducted

by our group, we found that a vast majority of patients (81%) had breakthrough dyspnea. Specifically, dyspnea affects patients' general activity, walking ability, normal work, sleep, mood, relations with others, and enjoyment of life (Reddy *et al.* 2009).

**B.2. The Current Management of Dyspnea**. The current management of dyspnea involves treatment of any reversible causes and supportive measures to minimize the sensation of dyspnea, including treatments such as oxygen, opioids, bronchodilators, and corticosteroids (Ben-Aharon *et al.* 2008, Cranston *et al.* 2008, Jennings *et al.* 2002). A majority of the studies on cancer-related dyspnea so far have focused on patients with dyspnea at rest. In a crossover randomized controlled trial, Bruera et al. compared subcutaneous morphine and placebo in 10 patients with advanced cancer who had dyspnea at rest. Subcutaneous morphine was found to be superior to placebo for relief of dyspnea (Bruera *et al.* 1993). This finding was replicated by Mazzocato et al. in another randomized controlled trial with similar design (Mazzocato *et al.* 1999). A Cochrane meta-analysis also showed a statistically significant positive effect of opioids on the sensation of breathlessness (p=0.0008), supporting the use of oral or parenteral opioids for treatment of dyspnea in patients with advanced disease (Jennings *et al.* 2002).

Although systemic opioids are established for management of dyspnea at rest, there are currently no evidence-based options for breakthrough dyspnea. In a case series, Bruera et al. reported the use of rescue morphine given subcutaneously for 312 episodes of breakthrough dyspnea in 45 cancer patients. After 30 minutes, 90% reported no to mild dyspnea (Bruera *et al.* 1993). Based on this study, most clinicians use a dose similar to the rescue opioid dose for breakthrough pain (i.e. 10-20% of total daily dose) to manage breakthrough dyspnea. However, a more recent double-blind randomized controlled trial comparing systemic fentanyl (oral or subcutaneous (SC)), nebulized fentanyl, and nebulized saline for breakthrough dyspnea found no significant difference in dyspnea relief at 10 minutes between the treatment arms (Charles *et al.* 2008). One of the reasons may be due to the short duration for the primary endpoint (10 minutes). To date, the evidence for opioid use for breakthrough dyspnea remains limited (Table 1). Further research is necessary to improve the management of this distressing and debilitating symptom.

**Table 1. Studies of Opioids for Breakthrough Dyspnea**

| Study | Methodology and patients | Agent and dose | Outcome |
|---|---|---|---|
| Bruera et al. Ann Intern Med 1993 (Bruera *et al.* 1993) | Prospective case series (45 cancer patients [pts]) | SC morphine 312 doses given (same dose as pain breakthrough) | After 30 minutes, 90% reported no-mild dyspnea; 5% mod-severe dyspnea |
| Benitez-Rosario et al. JPSM 2005 (Benitez-Rosario *et al.* 2005) | Retrospective case series (4 cancer pts) | OTFC 800mg/1200mcg 60mg/800mcg 120mg/600mcg 15mg/400mcg | RR decreased Dyspnea decreased by 90-100% in 20-60 minutes |

| | | | |
|---|---|---|---|
| Sitte et al. JPSM 2008 (Sitte and Bausewein 2008) | Retrospective case series (1 cancer pt, 2 heart failure pts) | Intranasal fentanyl 1/6 of MEDD | RR decreased, improved $O_2$ saturation in all 3 patients Dyspnea scores not reported |
| Gauna et al. JPM 2008 (Gauna *et al.* 2008) | Prospective case series (2 COPD pts, 2 cancer pts) 10 episodes | OTFC 30mg/200mcg 720mg/400mcg 20mg/200mcg 24mg/200mcg | RR decreased Dyspnea decreased by 90-100% in 20-60 minutes |
| Charles et al. JPSM 2008 (Charles *et al.* 2008) | Prospective, double blind crossover RCT (20 cancer pts) | Systemic hydromorphone Nebulized hydromorphone Nebulized saline | Dyspnea decreased similarly in all 3 arms (1.0, 0.9, 0.8) |

Abbreviations: RR=respiratory rate, OTFC=oral transmucosal fentanyl citrate, SC=subcutaneous

**B.3. Rapid Onset Opioids for Breakthrough Dyspnea.** The episodic and transient nature of breakthrough dyspnea makes fast onset opioids an attractive option. Administration of opioids intravenously or subcutaneously can allow rapid delivery of the drug, although many patients do not have access to these routes at home. Fentanyl is a highly lipophilic compound. Over the past decade, there has been active development of fentanyl, including delivery by the transmucosal (oral transmucosal fentanyl citrate [OTFC], Actiq), buccal (Fentora) and intranasal (Lazanda, Instanyl) formulations (Gordon and Schroeder 2008, Lecybyl and Hanna 2007). These fentanyl formulations have been successfully used to manage breakthrough pain (Christie *et al.* 1998, Coluzzi *et al.* 2001, Fallon *et al.* 2011, Farrar *et al.* 1998, Mercadante *et al.* 2007, Portenoy *et al.* 1999, Portenoy *et al.* 2006, Portenoy *et al.* 2010, Slatkin *et al.* 2007), although their role in breakthrough dyspnea has only been reported in a handful of studies. Two small retrospective case series reported on the use of transmucosal and intranasal fentanyl (Benitez-Rosario *et al.* 2005, Sitte and Bausewein 2008) and one prospective series examined the use of OTFC (Gauna *et al.* 2008) suggest significant improvement in breakthrough dyspnea with these agents. Randomized controlled trials are urgently needed to confirm these findings with rapid onset opioids, which could potentially open up a new therapeutic indication for these medications.

FPNS is a particularly attractive option for breakthrough dyspnea. It was approved by the US Food and Drugs Administration (FDA) in 2011 for breakthrough pain in opioid-tolerant patients with cancer, and represents an alternative delivery system for fentanyl in addition to the transdermal, parenteral, and transmucosal routes. Pharmacokinetic studies revealed that FPNS has a bioavailability of approximately 80% (Fisher et al. 2010, Fisher et al. 2010). The time to maximal effect (Tmax) was between 15-20 minutes (Fisher et al. 2010, Fisher et al. 2010). FPNS has been found in clinical trials to provide greater and more rapid pain relief and reduces pain better than placebo (Kress et al. 2009) and transmucosal fentanyl citrate (Mercadante et al. 2009).

## C. Experimental Approach

**C.1. Overall Study design.** This is an investigator initiated study supported in part by Depomed, Inc**.** We propose a 2-arm, double blind, parallel randomized controlled trial of FPNS and placebo for cancer patients with breakthrough dyspnea (Figure 1). The main goal of this study is to determine the effect size for both FPNS and placebo arm to inform a larger, adequately powered confirmatory randomized controlled trial. After study consent, eligible patients will be asked to complete a number of surveys and a 6-minute walk test at baseline, rest until they return to baseline dyspnea, and then do a second 6-minute walk test 20 minutes after they have been given either FPNS or placebo prophylactically. They will then rest again to return to baseline dyspnea, and then do another 6-minute walk test 20 minutes after repeating the same dose of either FPNS or placebo (with at least 30 minutes between the first and second dose). This design will allow testing of both single and repeated dosing on dyspnea under a double blind design.

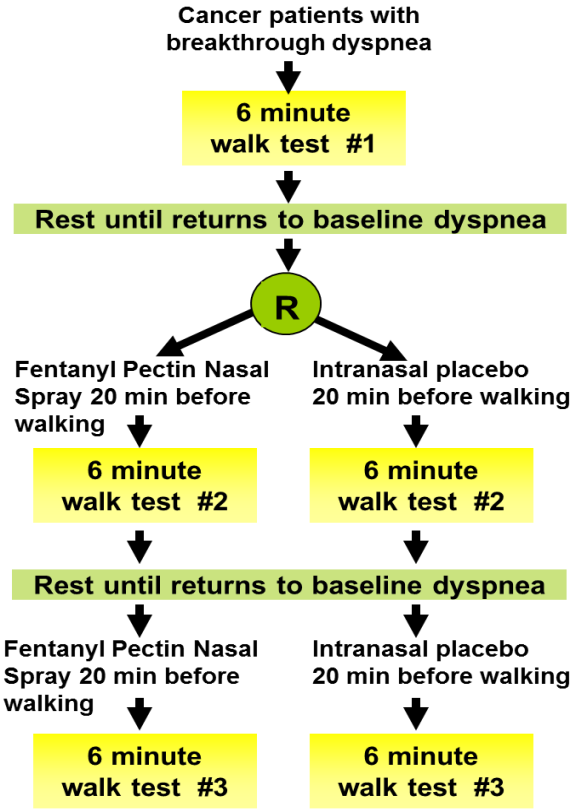


**Figure 1. Study Flow Chart**

Based on our experience conducting symptom control trials, this study will take between 1.5-2 hours to complete on a single visit. We believe this study design is feasible and would not add undue burden for patients. Patients will be compensated with a $50 gift card for their time and effort.

**C.2. Eligibility Criteria.** The eligibility criteria are shown in Table 2.

**Table 2. Study Eligibility Criteria**

**Inclusion Criteria**

1. Diagnosis of cancer
2. Breakthrough dyspnea, defined in this study as dyspnea on exertion with an average intensity level >=3/10 on the numeric rating scale
3. Outpatient at MD Anderson Cancer Center seen by the Supportive Care Service or Thoracic Medical Oncology
4. Ambulatory and able to walk with or without walking aid
5. On strong opioids with morphine equivalent daily dose of 80-500 mg, with stable (i.e. +/- 30%) regular dose over the last 24 hours
6. Karnofsky performance status >=50%
7. Age 18 or older
8. Able to complete study assessments

**Exclusion Criteria**

1. Dyspnea at rest >=7/10 at the time of enrollment
2. Supplemental oxygen requirement >6 L per minute
3. Delirium (i.e. Memorial delirium rating scale >13)
4. History of unstable angina or myocardial infarction 1 month prior to study enrollment
5. Resting heart rate >120 at the time of study enrollment
6. Systolic pressure >180 mmHg or diastolic pressure >100 mmHg at the time of study enrollment
7. History of active opioid abuse within the past 12 months
8. History of allergy to fentanyl
9. Unwilling to provide informed consent
10. Patients who currently have no evidence of disease

**C.3. Study screening.** A 2 step consent process will be used. First, a verbal consent will be obtained by the study staff to proceed with screening of potential participants for eligibility and to characterize their dyspnea using the dyspnea survey and the cancer dyspnea scale. Outpatients may be contacted by phone within 1 week prior to their scheduled clinic visit to informed them of this study so they can make necessary arrangements if interested in participating. Eligible patients will then be formally enrolled onto the study after they have signed the informed consent indicating a willingness for the patient to participate in the trial. The number of patients screened, approached, eligible and enrolled will be documented. Reasons for refusal for eligible patients will also be captured. Based on our experience with similar trials, we expect that a majority of patients will complete this study.

**C.4. Randomization.** A computer generated sequence in permuted blocks will be used to assign patients to either FPNS or placebo and provided via a secured website, stratified by baseline level of dyspnea NRS at rest at the time of enrollment (i.e. 0-3, 4-6). Biostatistics will set up a Randomization website. Investigational Pharmacy personnel will perform the randomization assignment.

**C.5. Blinding.** Both patients and the research staff conducting the assessment will be blinded to the treatment assignment. FPNS will be dispensed by Dispensing Pharmacy at MD Anderson. Placebo will be identical in appearance to the FPNS.

**C.6. Research staff.** An orientation will be held with research staff involved in this study to introduce them with the study design, and standardize the provision of each intervention.

**C.7. Study Interventions.** The supply of study medication (both FPNS and placebo) will be provided by Depomed, Inc. FPNS is FDA approved (NDA 022569/S-007) for treatment of breakthrough cancer pain in opioid-tolerant patients. Immediately upon patient enrollment, the study physician will be notified and will determine the morphine equivalent daily dose (MEDD) in real time using standardized equianalgesic ratios.

Based on clinical practice and similarly to the dose used for breakthrough pain, we will use an FPNS dose equivalent to 15-25% of the MEDD (Table 3). For patients randomized to receive FPNS, the study medication will be provided by Dispensing Pharmacy and will then be administered intranasally 20 minutes before the second 6-minute walk test. The same dose will be repeated at least 30 minutes after the first dose and 20 minutes prior to the third and final 6 minute walk test. We estimated the FPNS dose based on the following assumptions:

- A rescue dose of 15-25% of the MEDD is safe and adequate for relief of dyspnea (Bruera *et al.* 1993, Charles *et al.* 2008).
- FPNS has approximately 80% oral bioavailability (Fisher *et al.* 2010, Fisher *et al.* 2010).
- With repeat dosing 30 minutes apart, the maximum concentration (Cmax) for FPNS is approximately 1.6x higher than the first dose.

The modeled pharmacokinetic data for repeated dosing 30 minutes apart is shown in Figure 2. As a precautionary measure, patients will be asked to wait for 1 hour after completing the last walk before leaving MD Anderson. At the end of 1 hour, they will be assessed by our research staff before being released. If excessive drowsiness or adverse events occur, the study physician will assess the patients.

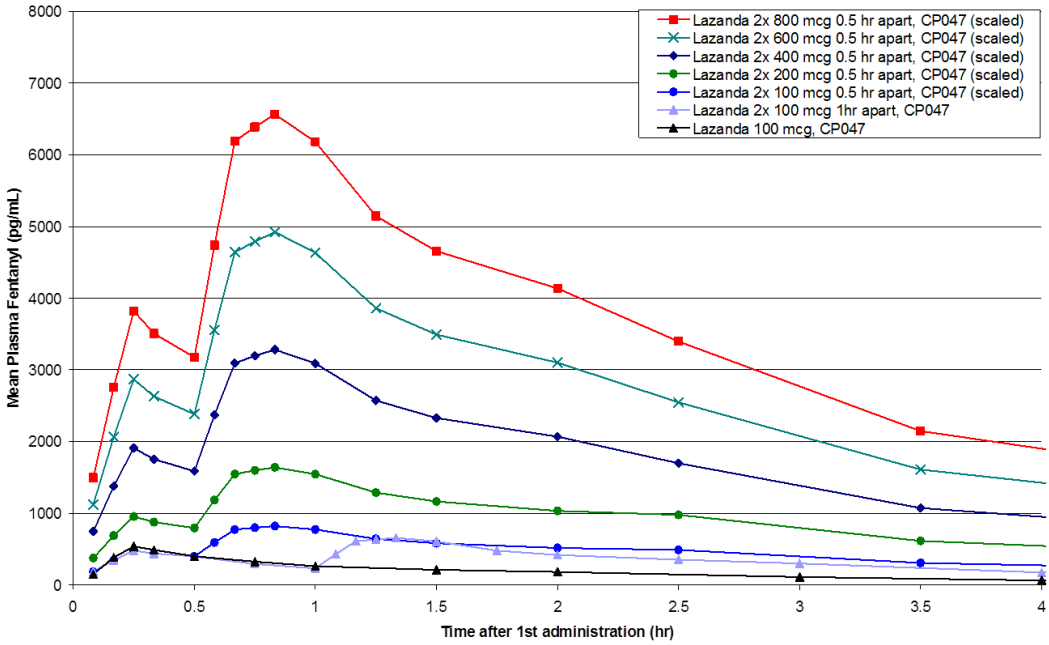


**Figure 2. Modeled Pharmacokinetic Data on Repeat Dosing of Fentanyl Pectin Nasal Spray after 30 m**

**Table 3. Dose of Fentanyl Pectin Nasal Spray Based on Morphine Equivalent Daily Dose[a]**

| Morphine equivalent daily dose (mg) | Total Fentanyl Pectin Nasal Spray Dose (mcg) | Number of FPNS sprays | Number of Placebo sprays |
|---|---|---|---|

| | | | |
|---|---|---|---|
| 80-159 | 100 | 1 (100 mcg in one nostril) | 1 |
| 160-239 | 200 | 2 (100 mcg in each nostril) | 2 |
| 240-319 | 300 | 3 (100 mcg in one nostril and 2 x 100 mcg in the other nostril)[b] | 3 |
| 320-540 | 400 | 4 (2 x 100 mcg in each nostril) | 4 |

[a] FPNS is available in 100 mcg.
[b] For the 300 mcg dose, patients will receive 1 spray in each nostril, then another spray again in the one of the nostrils.

Placebo will be identical in appearance to the FPNS, and given to patients 20 minutes before the second and the third 6-minute walk test. Both the patient and the research staff conducting the assessments will be blinded to the nature of the intervention. During this entire study, patients will be monitored closely by trained research staff, and will have rapid access to medical care if needed.

Because this involves only 2 doses given to opioid tolerant patients, and under close monitoring by trained staff, we believe the dosing schedule proposed is safe.

**C.8. Medication use during study.** To minimize the co-intervention effect on dyspnea, patients will be advised to avoid using breakthrough opioids (for any reason) or bronchodilators for at least 2 hours prior to and during the study.
**C.9. The 6-minute walk tests** will be conducted based on guidelines from the American Thoracic Society (Laboratories 2002). Walking aid and supplemental oxygen via nasal prongs are allowed as long as patients keep them the same as before enrollment and during the entire study. This walking test allows patients to rest if they need to, and is highly acceptable to patients. It provides important information regarding patients' functional status, exercise capacity, and health-related quality of life (Guyatt *et al.* 1985, Guyatt *et al.* 1985). Before and after each test, we will be assessing the (1) dyspnea level with numeric rating scale and Borg scale, and the (2) respiratory rate and oxygen saturation. After each test, we will also be assessing (1) the distance walked at the end of each minute or portion of, (2) the total walking time, (3) the level of dyspnea at the end of each minute or portion of (NRS and Borg scale), and (4) the average walking speed.

The 6-minute walk test has excellent short term reproducibility (Guyatt *et al.* 1985), as well as good face, construct, and predictive validity (Du Bois *et al.* 2011), and changes in this test are concordant with changes in symptoms and mortality (Olsson *et al.* 2005). The minimal clinical significant difference is found to be 24-45 m for patients with idiopathic pulmonary fibrosis (Du Bois *et al.* 2011), and 86 m for patients with COPD.

The first 6-minute walk test was designed to provide important information regarding a patient's level of dyspnea on exertion, and to facilitate intra-individual comparison since there is significant variability in the expression of dyspnea among patients.

**C.10. Variable rest period.** After the first and second 6 minute walk test, patients will be asked to sit down and rest. How long they rest would depend on when they return to baseline level of dyspnea numeric rating score + 1 or below (e.g. if baseline dyspnea = 4, they need to return to a level of 5 or less to qualify for next stage). During this rest period, patients will be assessed every 5 minutes to check their dyspnea level. If their dyspnea level met criteria and they feel ready to walk again, they will be given the study treatment and asked to wait for 20 minutes before they walk. At least 30 minutes should elapse between each dose of the study medication**.**

**C.11. Stopping rules.** Patients who do not develop any increase from their baseline dyspnea after the first 6-minute walk will not proceed to the next stage because of the lack of exercise induced dyspnea. If at any time during the study patients develop chest pain, severe leg cramps, staggering, diaphoresis, and/or dizziness, they will be asked to stop the study. If patients require more than 1 hour of rest and their dyspnea level still has not returned to baseline, they will also be taken off study. We plan to replace these patients and any other individuals who are not evaluable because they have not started the 2nd walk test.

**C.12. Study assessments.** See Table 4 for a detailed description of all study assessments.

**Table 4. Summary of Study Assessments**

| **Assessments** | **Base-line** | **Post 1st 6MWT** | **Rest #1** | **Pre 2nd 6MW** | **Post 2nd 6MW** | **Rest #2** | **Pre 3rd 6MW** | **Post 3rd 6MW** |
|---|---|---|---|---|---|---|---|---|
| Demographics and cancer diagnosis[1] | ✓ | | | | | | | |
| Medication history[2] | ✓ | | | | | | | |
| Karnofsky performance status[3] | ✓ | | | | | | | |
| Edmonton Symptom Assessment Scale[4] | ✓ | | | | | | | |
| Dyspnea Survey[5] | ✓ | | | | | | | |
| Cancer Dyspnea Scale[6] | ✓ | | | | | | | |
| $O_2$ saturation and respiratory rate | ✓ | ✓ | | ✓ | ✓ | | ✓ | ✓ |
| Dyspnea Numeric Rating Scale[7] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Dyspnea Borg scale[8] | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ | ✓ |
| Walking test parameters[9] | | ✓ | | | ✓ | | | ✓ |
| Adverse effects[10] | | | | ✓ | ✓ | | ✓ | ✓ |
| Neurocognitive testing[11] | | ✓ | | | ✓ | | | ✓ |
| Global assessment[12] | | | | | ✓ | | | ✓ |
| Blinding[13] | | | | | | | | ✓ |
| Patient satisfaction[14] | | | | | | | | ✓ |

[1] patient initials, medical record number, date of birth, sex, race, education, marital status, cancer diagnosis, co-morbidities, cause(s) of dyspnea.

[2] medications that could be used to treat dyspnea, including scheduled and as needed opioids, bronchodilators, and steroids will be documented.

[3] an 11-point assessment scale that rates patients' functional status between 0% (death) and 100% (completely asymptomatic) based on their ambulation, activity level, and disease severity (Schag *et al.* 1984).

[4] validated questionnaire that measures 10 common symptoms in the past 4 hours (pain, fatigue, nausea, depression, anxiety, drowsiness, shortness of breath, appetite, sleep, and feeling of well being) using numeric rating scales (Bruera *et al.* 1991).

[5] characterization of patients dyspnea including the following: presence of dyspnea at rest, average dyspnea in last 24 hours, worse dyspnea in last 24 hours, best dyspnea in last 24 hours, number of episodes of exacerbation per day, triggers of breakthrough dyspnea, average duration of each episode, current treatment for breakthrough dyspnea.
[6] validated 12-item questionnaire specifically designed to assess the quality of dyspnea in cancer patients during the past few days (Tanaka *et al.* 2000). Each item has a score between 1 and 5, for a maximum of 60. There are sub-scores for sense of effort, anxiety, and discomfort.
[7] a 0 (no dyspnea) to 10 (worst dyspnea) categorical scale validated for rating the severity of dyspnea (Dorman *et al.* 2007, Gift and Narsavage 1998, Powers and Bennett 1999). We will be measuring it every minute during the 6 minute walk test at 0, 1 min, 2 min, 3 min, 4 min, 5 min and 6 min (or end of walk).
[8] a 0 to 10 categorical scale for rating the severity of dyspnea. It is a ratio scale with descriptive anchors throughout the range in which a rating of 8 signifies breathlessness twice as severe as 4, which in turn is twice as severe as 2 (Dorman *et al.* 2007, Gift and Narsavage 1998, Kendrick *et al.* 2000, Powers and Bennett 1999). We will be measuring it 0 and 6 min (or end of walk) of each walk. The NRS will be administered before modified Borg scale.

[9] include the total distance walked, total walking time, the distance and time of first rest due to dyspnea, average walking speed.
[10] adverse effects related to the use of FPNS, such as dizziness, drowsiness, nausea, stuffy/blocked nose, runny nose, itching/sneezing, nose dryness, cough, sore throat, and taste disturbance will be assessed using a numeric rating scale from 0-10.
[11] patients will be asked to do finger tapping 10 and 30 sec, arithmetic, reverse memory of digits, and visual memory). This has been used in other studies by our group.(Bruera *et al.* 1992)
[12] patients will be asked about their dyspnea (worse, about the same, or better) comparing between the level of dyspnea between the first and second 6-minute walk tests (Guyatt *et al.* 1993, Redelmeier *et al.* 1996).
[13] blinding will be done by asking patients which group assignment they received: “FPNS”, “placebo”, or “do not know”.
[14] study satisfaction is assessed with the following questions, “Was it worthwhile for you to participate in this research study?”, “If you had to do it over, would you participate in this research study again?”, “Would you recommend participating in this research study to others?”, “Did you quality of life get better by participating in this research study?”, “Did you quality of life get worse by participating in this research study?”

**C.13. Feasibility data.** In addition to clinical outcomes, we will also collect feasibility data in this study Rates of recruitment and retention (% of subjects able to complete the study)

- Reasons for refusal and dropout
- Outcome measure—we will compare the sensitivity of Numeric rating scale and Borg scale to change, and identify key measure for future study
- Participant satisfaction—participants will provide an opinion regarding their satisfaction with study overall

**C.14. Patient Safety, Monitoring, and Confidentiality.** During the study, trained research staff will be performing study assessments and monitoring the patients carefully throughout the study period. A study physician will also be available by pager to address any concerns, distress or questions, and will attend to the patient as needed. Patients will be doing the test in a hallway outside the Supportive Care Center which typically does not have a lot of traffic, and will have immediate access to medical and nursing care if needed. See stopping rules below for further details. With the planned

doses of fentanyl in opioid-tolerant patients, we do not expect any significant side effects.

Regulatory monitoring will be provided by the principal investigator, the Institutional Review Board (IRB), and the Data Safety and Monitoring Board (DSMB). Patient confidentiality will be ensured by use of study numbers, secure storage of clinical data, and anonymous reporting.

## D. Statistical Analysis

**D.1. Sample Size Calculation.** Patients who have started the second walk test will be considered evaluable for this study's primary endpoint. 10 evaluable patients in the fentanyl arm provides 80% power to detect an effect size as small as 1.0 when alpha=5% using a two-sided paired t-test to compare dyspnea between the first and second walk tests. Results from this study will be used to calculate the sample size for an adequately powered randomized controlled trial.

**D.2. Data Analysis.** Summary descriptive statistics will be provided for demographics, outcomes, and other collected variables and will include proportions, medians, means, 95% confidence intervals, and other simple statistics as appropriate for the measure. Comparisons within arms will be performed using paired t-tests or signed rank tests.

## E. Data Confidentiality Procedures

Health information will be protected and we will maintain the confidentiality of the data obtained from the patient's chart.

Collection of identifiers: We will collect and securely store patients' identifiers (including name, medical record number and demographic specifications). Each patient will be assigned a study number that will be the only identifier to figure in the analytical file and personal data will not be disclosed in any form. The key linking these numbers will be retained in a securely locked file by the investigator.

Data Storage: Protection of electronic and paper records will be guaranteed. All electronic records will be stored on password-protected institution computers behind the institution firewall. Any paper records will be classified and stored in locked files inside a locked office.

Training of personnel: Only MDACC personnel trained in maintaining confidentiality, the principle investigators and co-investigators, will have access to study records.

Data sharing: Study data will not be shared with any individuals or entities. The data will be kept by the principle investigator in a locked file cabinet.

Final disposition of study records: These data will be used only for this research study data files will be destroyed 5 years after publication of the findings.

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