



# THE TABLET: PALLIATIVE CARE PHARMACY TIPS

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## TODAY'S TOPIC:

### Fentanyl for Dyspnea in Palliative Care Patients

#### Background:

Dyspnea is one of the most common symptoms reported in patients with terminal cancer in the last six months of life. The most common presentation of dyspnea is on exertion, limiting patients' functioning. Opioids are the most studied & employed class for relieving dyspnea. Due to its rapid-onset and wide-range of available formulations, fentanyl is a treatment option for opioid-tolerant patients. Formulations include nebulized, pectin nasal spray, buccal tablets, and sublingual spray.

**Previous studies** have examined the effects of different fentanyl formulations on dyspnea. A 2014 RCT examined the effects of prophylactic subcutaneous fentanyl on exercise-induced dyspnea in cancer patients.<sup>1</sup> Results showed a significant improvement in dyspnea intensity, fatigue, and walk distance. A 2019 retrospective study also examined the effects of subcutaneous fentanyl on dyspnea in a cohort of advanced cancer patients.<sup>2</sup> The authors concluded that subcutaneous fentanyl may be associated with dyspnea relief in palliative care patients, however further research is required. Areas of research include the benefits of easier to use formulations such as sublingual or buccal film, and an optimal dosing regimen. A 2019 RCT examined the effects of a high-dose and low-dose fentanyl sublingual spray for dyspnea in cancer patients, highlighted below.<sup>3</sup>

#### Importance:

Dyspnea is one of the most common symptoms affecting quality of life among terminally ill cancer patients & the second most common reason to initiate palliative sedation. Despite the prevalence of dyspnea in palliative care patients, much remains unknown about the optimal opioid regimen for managing dyspnea. Reviewing novel drug formulations can provide palliative care clinicians options in treating this symptom.

#### The Literature:

[J Pain Symptom Manage. 2019 Oct;58\(4\):605-613.](#)

#### Prophylactic Fentanyl Sublingual Spray for Episodic Exertional Dyspnea in Cancer Patients: A Pilot Double-Blind Randomized Controlled Trial

##### Methods:

- Parallel, dose-finding, double-blind randomized clinical trial, opioid-tolerant cancer patients
- Shuttle walk test (SWT) at baseline and then a second shuttle walk test 10 minutes after receiving a single dose of fentanyl sublingual spray (FSS) equivalent to either 35%-45% (high dose) or 15%-25% (low dose) of the total daily opioid dose

**Objectives:** Examine the effect of two doses of prophylactic Fentanyl sublingual spray on exertional dyspnea

##### Outcomes:

- Primary outcome: change in modified dyspnea Borg scale (0-10) between the first and second shuttle walk test
- Secondary outcomes: changes in walk distance, vital signs, neurocognitive function, and adverse events.

**Results:** n=30; average age: 52 years (range 22-77); 67% female

- High-dose FSS (n=13) resulted in a significant within-arm reduction between the first & second SWT in dyspnea intensity (mean change -1.4)
- The SWT distance significantly increased in both the high-dose (43.7 m) and low-dose (24.2 m)
- High-dose FSS did not result in more adverse effects relative to low-dose FSS.

Variable	High-Dose Group, Mean (SD) [95% CI]				Low-Dose Group, Mean (SD) [95% CI]			
	First Walk	Second Walk	Difference	Pvalue <sup>a</sup>	First Walk	Second Walk	Difference	Pvalue <sup>a</sup>
<b>Modified Borg Scale: Dyspnea Intensity (primary outcome)</b>								
Beginning of walk	0.6 (0.8)	0.7 (1.0)	0.1 (0.5)	0.44	0.5 (0.7)	0.4 (0.8)	-0.06 (0.6)	0.84
End of walk	5.1 (1.1)	3.8 (1.4)	-1.3 (1.6)		5.1 (2.0)	4.5 (2.1)	-0.5 (1.4)	
Difference	4.5 (1.7)	3.1 (1.5)	-1.4 (1.6)	0.007	4.6 (1.7)	4.1 (2.2)	-0.5 (1.6)	0.24
			[-2.4, -0.5]				[-1.3, 0.3]	
Difference/ distance walked (/100 m)	1.5 (0.9)	0.9 (0.7)	-0.6 (0.5)	<0.001	1.6 (0.9)	1.3 (0.7)	-0.3 (0.5)	0.03
			[-0.9, -0.3]				[-0.6, -0.1]	
Difference/min walked (/min)	0.8 (0.3)	0.5 (0.3)	-0.3 (0.3)	<0.001	0.8 (0.3)	0.7 (0.4)	-0.1 (0.2)	0.05
			[-0.4, -0.1]				[-0.3, -0.008]	
<b>Modified Borg Scale: Dyspnea Unpleasantness</b>								
Beginning of walk	0.6 (0.8)	0.7 (1.3)	0.1 (0.7)	0.94	0.4 (1.0)	0.4 (1.0)	-0.03 (0.3)	>0.99
End of walk	3.9 (1.7)	2.9 (1.9)	-1.0 (1.9)		4.1 (2.4)	3.4 (2.8)	-0.7 (1.3)	
Difference	3.3 (2.0)	2.2 (1.8)	-1.0 (1.8)	0.06	3.7 (2.1)	3.0 (2.5)	-0.6 (1.4)	0.10
Walk distance (m)	354.6 (155.8)	398.3 (148.7)	43.7 (30.0)	0.001	343.2 (148.4)	367.4 (159.6)	24.2 (35.7)	0.01
			[25.6, 61.8]				[5.8, 42.6]	
Walk time (min)	6.2 (1.9)	6.7 (1.7)	0.5 (0.4)	<0.001	6.0 (1.9)	6.3 (1.8)	0.3 (0.4)	0.009
			[0.3, 0.7]				[0.18, 0.5]	

##### Discussion:

- These results are consistent with previous clinical trials involving fentanyl pectin nasal spray and buccal tablets
- This study had several limitations, including recruitment of patients from a single tertiary cancer center, having a relatively high-performance status, patients needing to be opioid-tolerant, and patients only received a single dose of FSS

**Conclusion:** Prophylactic FSS demonstrated a dose-response relationship in improving dyspnea and walk distance.

#### Bottom Line:

- Previous research has shown fentanyl as a potential treatment option that has shown benefit for palliative care patients experiencing dyspnea
- High-dose FSS showed a significant reduction in dyspnea intensity & an increase in SWT distance, indicating a *functional* benefit for patients. This is great! Although, I wonder if this study is generalizable to our typical oncologic population, given the distances these patients walked, assuming they are potentially more functional at baseline than most of our patients
- This trial was limited to opioid-tolerant patients, so it is unclear if this would be a safe option for our opioid naïve patients
- Fentanyl has a quick onset of action making it a potentially favorable option for our patients. There are further areas of research needed in this area of study, including: efficacy compared to other PO opioids, optimal dose for opioid-naïve patients, and tolerability for multiple doses
- Availability of sublingual fentanyl spray (ie. insurance coverage) could be a barrier to this being a feasible treatment option for our patients

#### References:

1. Hui D, Xu A, Frisbee-Hume, et. al. Effects of Prophylactic Subcutaneous Fentanyl on Exercise-Induced Breakthrough Dyspnea in Cancer Patients: A Preliminary Double-Blind, Randomized Control Trial. *J Pain Symptom Manage.* 2014 Feb;47(2):209-217.
2. Benitez-Rosario M, Rosa-Gonzalez I, Gonzalez-Davila E, et. al. Fentanyl Treatment for End-of-Life Dyspnea Relief in Advanced Cancer Patients. *Support Care Cancer.* 2019;27:157-164.
3. Hui D, Hernandez F, Larsson L, et. al. Prophylactic Fentanyl Sublingual Spray for Episodic Exertional Dyspnea in Cancer Patients: A Pilot Double-Blind Randomized Control Trial. *J Pain Symptom Manage.* 2019 Oct;58(4):605-613.

**CLINICAL PEARL:** Fentanyl, like other opioids, has been shown to be an effective option in improving dyspnea in palliative care patients. Limitations for its use may exist in clinical practice.