Original Article

Effect of Opioid Exposure on Efficacy and Tolerability of Sublingual Fentanyl and Subcutaneous Morphine for Severe Cancer Pain Episodes. Secondary Analysis From a Double-Blind Double-Dummy, Randomized Trial

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Abstract

Context. Few studies have addressed the impact of previous opioid exposure on the effect of opioids for the treatment of severe cancer pain episodes.

Objectives. We aimed to test whether previous exposure to higher opioid doses was associated with a reduced analgesic effect of fentanyl sublingual tablets (FST) and subcutaneous morphine (SCM) and whether it had an influence on their relative effect.

Methods. This is a secondary analysis of a placebo-controlled randomized trial comparing 100 μg FST with 5 mg SCM for the acute treatment of severe cancer pain episodes. The effect of previous opioid exposure (oral morphine equivalent daily dose from 20 to 120 mg) on pain intensity difference (PID) and side effects at 30 and 60 minutes after administration (PID 0−30 minutes, PID 0−60 minutes, and adverse events 30−60 minutes) and on re-medication for inefficacy, was studied by multivariable linear and logistic regression models and statistical tests for interaction.

Results. A total of 114 patients were enrolled. Results indicate modest and nonstatistically significant effect of previous opioid exposure on all the outcomes examined ($P = 0.11$, $P = 0.35$, $P = 0.07$, and $P = 0.52$, respectively, for PID 0−30 minutes, re-medication, PID 0−60 minutes, and adverse events 30−60 minutes). Nonstatistically significant tests for interaction for all models indicated a lack of impact of previous opioid exposure on the difference in the analgesic effect between treatments.

Conclusion. In this study, we could not demonstrate an effect of previous opioid exposure, from 20 to 120 mg oral morphine equivalent daily dose, on the absolute and relative efficacy and tolerability of 100 μg FST and 5 mg SCM for severe cancer pain episodes. J Pain Symptom Manage 2019;58:587−595. © *2019 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. All rights reserved.*

Key Words
Fentanyl, morphine, cancer pain

Introduction

Effective cancer pain management is based on the regular "around the clock" use of opioid analgesics in combination with "as needed" or "rescue" opioid extra doses[1,2] to facilitate opioid dose titration and to treat severe pain episodes, often described as breakthrough pains, which are not controlled by baseline therapy.[3–5]

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Oral immediate release opioids can be used "as needed" for the treatment of severe pain episodes, but their pharmacokinetics and pharmacodynamics may not be appropriate for pain exacerbations of fast onset and short duration;[2,6] more recently, transmucosal fentanyl formulations for oral or nasal administration have been specifically developed to treat severe pain episodes.[7] Two double-blind randomized controlled trials (RCTs)[8,9] and two open-label trials[10,11] have proved superiority of transmucosal fentanyl formulations over immediate-release oral morphine. One open-label RCT compared parenteral morphine with oral fentanyl lozenges, showing superior analgesia of morphine at 15 minutes after administration and nonsignificant differences at 30 minutes.[12] These transmucosal fentanyl formulations have been investigated and registered for use in opioid-tolerant adult patients.[13–15]

It is known that tolerance develops in chronic opioid administration, and in fact, patients with chronic cancer pain can tolerate doses of opioids, which would be dangerous in all other circumstances.[16] It is common clinical practice to adapt the patients' overall opioid dose in time, titrating it to effect; this process includes both the around the clock daily dose and the amount given as rescue dose to treat pain exacerbations. Guidelines suggest using one-sixth or 20% of the daily opioid consumption as a rescue dose in the case of oral morphine.[2] The availability of transdermal fentanyls has renewed the interest in establishing a safe and effective dose for each patient. Two apparently contradicting practical clinical guidelines emerged, one favoring the choice of a fentanyl dose which is proportional to the patient previous opioid dose exposure and the other one suggesting to start with the minimum available fentanyl dose and then to titrate it to effect in subsequent clinical episodes when clinically required. A few studies have addressed the potential impact of previous opioid exposure on transmucosal fentanyl formulations efficacy and tolerability, also considering that a number of cancer patients with pain are treated with relatively low opioid doses.[17,18]

In a double-blind RCT, we compared the analgesic efficacy of 100 μg fentanyl sublingual tablets (FST) with 5 mg of subcutaneous morphine (SCM).[19] This trial showed a slight difference in favor of SCM, which was over the pre-established noninferiority limit and an equal percentage of patients (71%) achieving clinically meaningful analgesia (i.e., a reduction of 33% pain intensity) at 30 minutes. Both drugs were very well tolerated and 93% of patients preferred the sublingual administration. Patients enrolled in the trial were consuming different doses of regularly administered opioids (range 20–120 mg of oral morphine equivalent daily dose [OMEDD]) for different periods.

We present here secondary analyses from the latter trial[19] to test whether previous exposure to higher opioid doses was associated with a reduced analgesic effect of FST and SCM and whether it had an influence on their relative efficacy.

Methods

The data are from a double-blind, double-dummy, parallel-group, RCT aimed at testing noninferiority of FST vs. SCM.[19] The study, registered in the EudraCT database (2013-003319-23), was conducted at the outpatient Palliative Care Clinic at the Fondazione IRCCS Istituto Nazionale Tumori of Milan and received institutional review board's approval (INT 123/13). All patients provided written informed consent before study enrollment.

Main eligibility criteria were as follows: current pain ≥6 on a 0–10 numerical rating scale (NRS) assessed at the time of the visit; controlled pain in the previous 24 hours ≤4 on a 0–10 NRS; stable around the clock daily opioid consumption from 20 to 120 mg OMEDD in the previous three days. Patients were excluded if previously treated with transmucosal fentanyl formulations, if they were cognitively impaired, and if they had severe hepatic (Child-Pugh score = C) and/or renal failure (serum creatinine level ≥1.5 times the upper normal limit).

Patients were randomly assigned to receive either 100 μg FST plus placebo or 5 mg SCM plus placebo. The doses chosen are discussed in the conclusions.

Patients were allocated to treatment using 1:1 random block randomization and stratified by around the clock opioid dosage (OMEDD of 20–60 mg vs. 60–120 mg).

Pain intensity was measured using the "pain right now" item of Brief Pain Inventory short form questionnaire.[20] It was assessed immediately before the drug administration and then after 10, 20, 30, and 60 minutes. Patients not reaching satisfactory analgesia at 30 minutes were offered a second dose of the same drug. Adverse events (AEs) including somnolence, difficulty concentrating, nausea, vomiting, dry mouth, confusion, muscle spasms, stomachache, difficulty urinating, difficulty breathing, and itching were registered at 30 and 60 minutes after the drug administration on four-point verbal rating scales using the Therapy Impact Questionnaire.[21] Full details of the study methods are reported in the primary publication.[19]

Power Considerations and Statistical Analysis

Power analysis was based on the main noninferiority aim of the study[19] and no power calculation for the analyses presented here was carried out, as this was a secondary aim. The following are the end points considered in

the present analyses: pain intensity difference (PID) between baseline and the average of "pain right now" scores in the first 30 minutes (PID 0−30 minutes), proportion of patients needing a second dose of opioid for inefficacy (re-medication), PID between baseline and the average of "pain right now" scores in the first 60 minutes (PID 0−60 minutes), and average of AE intensity scores at 30 and 60 minutes.

We applied multivariable linear regression models to analyze the association of previous opioid exposure with PID (PID 0−30 minutes and PID 0−60 minutes) and AE intensity scores; risk of re-medication at 30 minutes (yes/no) was analyzed using logistic regression models. All models included study treatment as dependent variable; models on re-medication were adjusted by baseline pain intensity score, and the one on PID 0−60 minutes as was adjusted by both baseline pain intensity score and re-medication. Statistical tests for interaction between treatment and opioid exposure were used to assess the potential impact of the latter on the relative efficacy of FST and SCM (i.e., whether the comparison between FST and SCM resulted different across different baseline opioid dosages).[22] To avoid potential loss of information, risk of misclassification or bias in the results,[23] opioid exposure was treated as a continuous variable in regression models (divided by 20 to improve regression coefficients interpretability). However, in some tables and figures, it was categorized as low (OMEDD 20−30 mg), medium (OMEDD 31−70 mg), and high (OMEDD 71−120 mg) for descriptive purposes. Results were reported in terms of mean and SD values, beta values, risk difference values (RDs), Type I probability error (P), and 95%CIs. All statistical analyses were performed using Stata 14 (StataCorp, College Station, TX); RDs estimated the post-estimation command adjrr.[24]

Results

A total of 114 patients were enrolled in the original study and randomized to either FST (58 patients) or SCM (56 patients). One patient (FST group) did not receive the study drug because of consent withdrawal and was excluded from the analysis. One hundred and ten patients completed all post treatment assessments. One patient (FST group) withdrew before 30 minutes for inefficacy, and two patients (one in each group) missed assessment at 60 minutes. All of them were included in the analysis using available data approach. Detailed CONSORT flow chart diagram has been previously reported.[19] Table 1 describes basic clinical and pain-related characteristic of the study sample by low, medium, and high opioid dosage levels (respectively, 47, 35, and 31 patients). Most patients had Karnofsky performance status between 70 and 80 and somatic pain was the most common pain type. As expected, patients in the low dosage group were more frequently taking World Health Organization Step II opioids. The two treatment groups resulted balanced on most patient characteristics including previous opioid exposure (54.6 vs. 54.2 mg OMEDD, respectively, in FST and SCM groups—data not reported in table[19]). Patients had been treated with opioids for a median of 53 days (interquartile range 17−149 days), and only six patients had been consuming opioids for less than seven days (one patient for four days and five patients for six days). They had been consuming the last opioid prescribed for a median of 13 days (interquartile range 7−28 days).

Reduction in the average of pain scores (0−10 NRS) in the first 30 minutes after study drug administration were 2.6 and 3.1, respectively, for FST and SCM; re-medication for inefficacy was needed in 51% and 37% of patients on FST and SCM, respectively.[19]

Multivariable regression models (Table 2) indicate modest and nonstatistically significant effect of previous opioid exposure on all the outcomes examined: an increase of 20 mg in previous opioid exposure was associated to a slightly smaller PID 0−30 minutes (−0.14, 95% CI = −0.31 to 0.03, $P = 0.11$) and PID 0−60 minutes (−0.15, 95% CI = −0.31 to 0.01, $P = 0.07$), a slightly higher likelihood of re-medication for inefficacy (RD = 2%, 95% CI = −2% to 7%, $P = 0.35$), and no difference on average AEs intensity (−0.01, 95% CI = −0.01 to 0.03, $P = 0.52$).

Despite nonstatistically significant, the results do not allow to rule out a potential limited reduction of efficacy with both fentanyl and morphine associated with increasing previous opioid exposure. In fact, the lower 95% CI bound of −0.31 in PID 0−30 minutes and PID 0−60 minutes for each OMEDD 20 mg increase could justify a diminished analgesic effect of 1.5 on a 0−10 NRS in patients taking 120 mg OMEDD compared with those taking 20 mg OMEDD. Concurrently, each 20 mg OMEDD increase in opioid exposure is associated with an increased risk of re-medication after sublingual fentanyl (SLF) or SCM (RD = 2%); again, the upper 95% CI = 7% for the RD indicates that our data are compatible with an increased risk of re-medication up to 36% in a dose range from 20 to 120 mg OMEDD. The scatter plots reported in Fig. 1 describe the slightly negative, yet nonsignificant, association between treatment response (PID 0−30 minutes) and previous opioid exposure for both FST and SCM, as emerged from the regression analyses.

Previous opioid exposure by treatment interaction was also tested in each model presented, but was never significant (Table 2, last column); this indicates a lack of impact of previous opioid exposure on the difference in the analgesic effect between treatments. This is graphically shown in Fig. 2 for PID 0−30 minutes.

Table 1
Baseline Clinical and Pain Characteristics of the Study Sample According to Previous Opioid Exposure

	Previous Opioid Exposure		
	Low 20–30 mg ($N = 47$)	Medium 31–70 mg ($N = 35$)	High 71–120 mg ($N = 31$)
Characteristic	N (%)	N (%)	N (%)
Gender			
Female	22 (46.8)	19 (54.3)	17 (54.8)
Male	25 (53.2)	16 (45.7)	14 (45.2)
Age			
Mean	56.2	64.1	61.2
SD	12.1	13.3	10.6
Karnofsky performance status			
60	2 (4.3)	2 (5.7)	2 (6.5)
70	14 (29.8)	9 (25.7)	6 (19.4)
80	24 (51.1)	15 (42.9)	12 (38.7)
90	7 (14.9)	9 (25.7)	11 (35.5)
Pre-treatment pain intensity[a]			
Mean	7.7	7.5	7.4
SD	1.5	1.5	1.2
Pain type[b]			
Somatic	39 (83.0)	29 (82.9)	24 (77.4)
Visceral	9 (19.1)	6 (17.1)	6 (19.4)
Neuropathic	20 (42.6)	21 (60.0)	10 (32.3)
Around the clock analgesic medication			
Codeine	23 (48.9)	1 (2.9)	0 (0.0)
Tramadol	6 (12.8)	3 (8.6)	0 (0.0)
Morphine	2 (4.3)	3 (8.6)	2 (6.4)
Fentanyl	0	9 (25.7)	11 (35.5)
Oxycodone	16 (34.0)	17 (48.6)	11 (35.5)
Hydromorphone	0	1 (2.9)	0
Tapentadol	0	1 (2.9)	7 (22.6)
Adjuvant analgesic drugs			
No	20 (42.5)	15 (42.9)	10 (32.3)
Yes	27 (57.5)	20 (57.1)	21 (67.7)

NRS = numerical rating scale.
[a]0–10 NRS.
[b]More than one type is possible.

With estimated differences ranging from −0.63 to −0.22 (the different dots correspond to doses from 20 to 120 mg), this figure indicates that the discrepancy in the effect between FST and SCM (between-treatment PID) does not significantly vary at different opioid dosages.

Table 3 reports average AE intensity scores of all symptoms separately. Average values all below 1 (corresponding to "A little") indicate a good tolerability of both FST and SCM at different levels of baseline opioid exposure. To give a descriptive overview of a potential effect on tolerability due to re-medication, Fig. 3 reports average intensities of four among the most common opioid-related AEs at 60 minutes, according to treatment, previous opioid exposure and re-medication at 30 minutes. No relevant differences in AEs intensity scores by re-medication were found.

Discussion

In patients regularly taking opioids at dosages from 20 to 120 mg OMEDD, we found no statistically significant effect of previous opioid exposure on the absolute and relative efficacy and tolerability of FST and SCM for severe pain episodes. The results also indicate a limited and well tolerable intensity of AEs in patients treated with low dosages of opioids as well as in patients in need of re-medication at 60 minutes. In fact, side effects average intensities never exceeded the level of "A little" on a four-level verbal rating scale (Table 3 and Fig. 3).

Our results are only partly in agreement with previous evidence. A relationship between previous opioid dose exposure, tolerance, and the dose of single transmucosal fentanyl needed to treat breakthrough pains was shown in a subgroup analysis from one open-label randomized trial;[25] in patients using more than 120 mg OMEDD, the analysis showed better pain control (i.e., more patients with a decrease in pain intensity ≥50% and less need of re-medication) when using a proportional initial dosing of SLF vs. a fixed 100 μg dose. However, this difference was not found when looking at the whole patient sample ($N = 80$) in the study. Conversely, in a metanalysis of clinical trials on oral transmucosal fentanyl citrate, Hagen et al.[26] could demonstrate a statistically significant, yet low, correlation between the

Table 2
Linear and Logistic Regression Models Testing the Effect of Baseline Opioid Dose on Analgesic Efficacy and Tolerability

		Regression Models		
		Without Interaction		With Interaction
Outcomes	*N*	Treatment Effect (SCM respect to FST)	Previous Opioid Exposure Effect[a]	Treatment by Previous Opioid Exposure Interaction
Pain intensity difference 0–30 minutes[b]	113			
Linear model				
Beta		0.49	−0.14	−0.08
95% CI		−0.09 to 1.07	−0.31 to 0.03	−0.43 to 0.26
P-value		0.09	0.11	0.64
Re-medication for inefficacy at 30 minutes[c]	113			
Logistic model				
Risk difference		−13%	2%	−0.21[d]
95% CI		−30% to 3%	−2% to 7%	−0.71 to 0.29
P-value		0.11	0.35	0.41
Pain intensity difference 0–60 minutes[e]	113			
Linear model				
Beta		0.32	−0.15	−0.01
95% CI		−0.21 to 0.85	−0.31 to 0.01	−0.02 to 0.01
P-value		0.23	0.07	0.28
Adverse event score[f]	112			
Linear model				
Beta		0.03	0.01	0.00
95% CI		−0.03 to 0.1	−0.01 to 0.03	−0.04 to 0.04
P-value		0.30	0.52	0.83

FST = fentanyl sublingual tablets; SCM = subcutaneous morphine; NRS = numerical rating scale.
[a]Baseline opioid dosage in steps of 20 mg.
[b]Pain intensity difference between baseline and average of 0–30 minutes scores (0–10 NRS). Positive values indicate improvement. Linear regression model.
[c]Consumption of a second dose of drug at 30 minutes for inefficacy—logistic model adjusted by baseline pain intensity score.
[d]Beta value of logistic regression was reported for interaction term.
[e]Pain intensity difference between baseline and average of 0–60 minutes scores (0–10 NRS). Positive values indicate improvement. Linear regression model adjusted by baseline pain intensity score and re-medication.
[f]Adverse event score: average of 30 and 60 minutes assessments (0–3 verbal rating scale; 0 = No, 1 = A little, 2 = Much, and 3 = Very much). Linear regression model adjusted by baseline pain intensity score and re-medication.

previous exposure to opioids, and the analgesic effective analgesic dose of fentanyl transmucosal doses after titration, in a population of 188 patients with cancer pain and a much more variable previous opioid exposure. The authors also pointed out that the extremely high variability at the individual level suggests that this association has little clinical impact not modifying the need of individual titration of the fentanyl dose. Within an opioid exposure range from 20 to 120 mg OMEDD, our results do not support specific proportionality between previous opioid exposure and analgesic effect. However estimates variability (extreme values of the 95% CIs in Table 2) do not rule out the possibility of such a relationship at higher doses.

In this study, 100 μg SLF were compared in acute administration with 5 mg SCM; the choice of the two drug doses deserve a comment. As there is no direct comparison between parenteral morphine and SLF after acute administration, the doses were chosen based on their reasonable correspondence to clinical practice and on pharmacological considerations. To determine the "as needed" dose, guidelines recommend the use of one-sixth or 20% of the daily opioid requirement.[2] In our patient population, with opioid exposure from 20 to 120 mg OMEDD, this would correspond to a range from 1.3 mg (unlikely to be clinically meaningful) to 8 mg of parenteral morphine, and to 4 mg parenteral morphine in a patient with 60 mg OMEDD.

Parenteral fentanyl (IV) is known to be 100 times more potent than morphine, therefore 50 μg would correspond to 5 mg IV morphine.[27] Bioavailability data on the 100 μg SLF tablet used in this trial are limited to producer company information, suggesting a total bioavailability of 57%,[28] whereas 67% bioavailability is reported for a different buccal fentanyl preparation.[29] Registered drug prescribing requirements indicate to administer 100 μg dose to patients with previous opioid exposure equal to 60 mg OMEDD or higher, and subsequently to titrate to effect. Finally, one experimental pain model in healthy volunteers suggests that 4.8 mg of IV morphine can be equianalgesic to 100 μg of buccal fentanyl, but with very wide confidence intervals of the estimated ratio.[30] It is

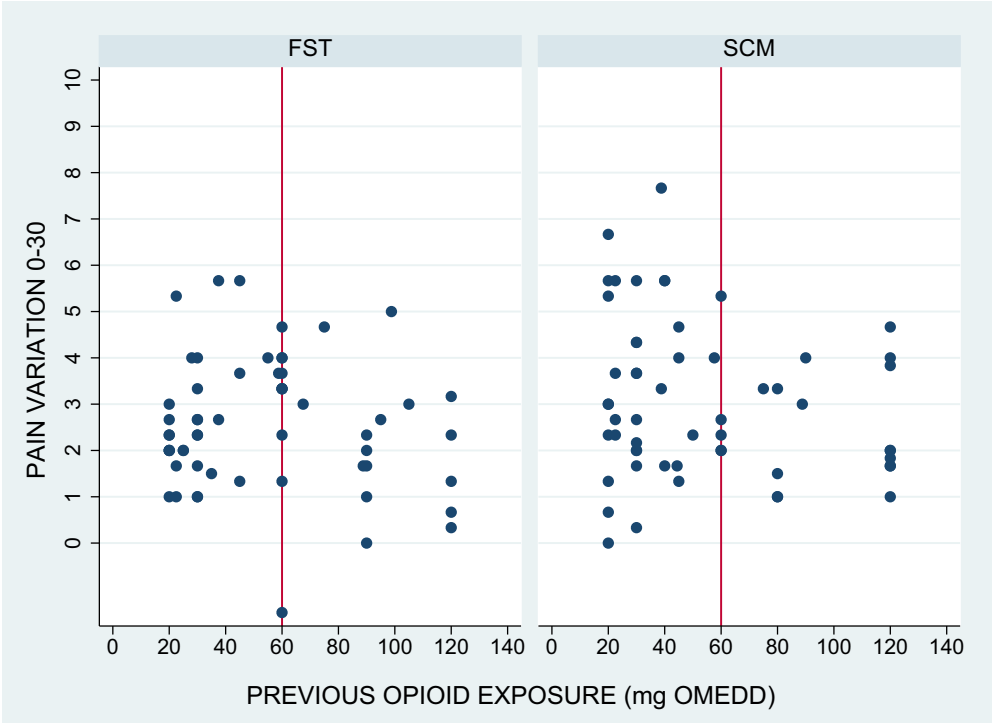

Fig. 1. Scatter plots of average pain intensity reduction in the first 30 minutes (PID 0–30 minutes) and previous opioid exposure, by study treatment. PID = pain intensity difference; FST = fentanyl sublingual tablets; SCM = subcutaneous morphine; OMEDD = oral morphine equivalent daily dose.

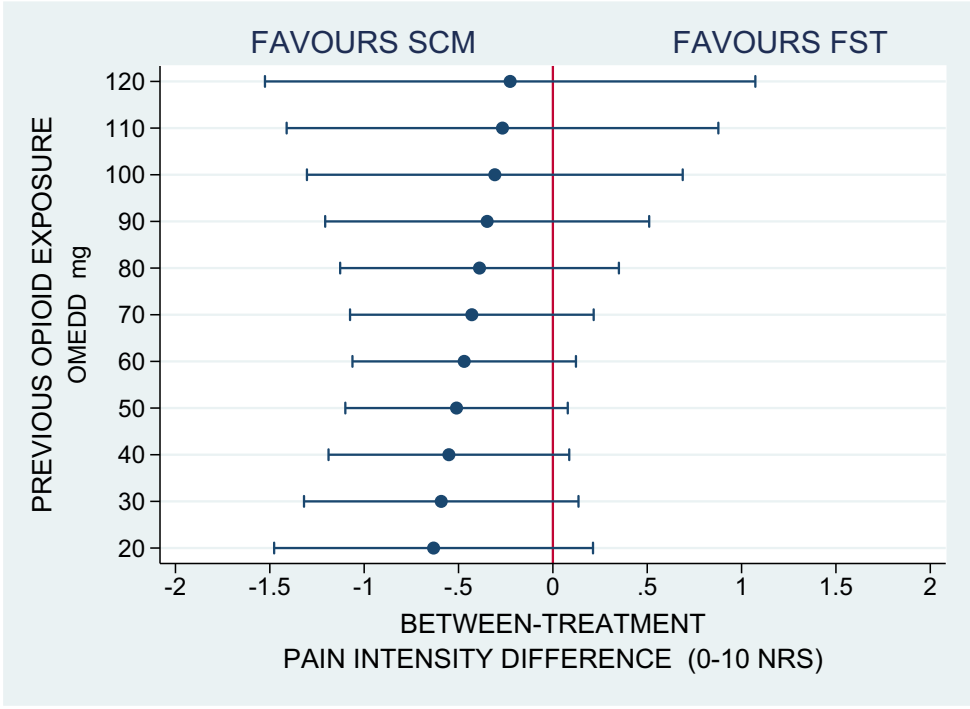

Fig. 2. Between-treatment pain intensity differences (point estimates, dots, and 95% CIs) at different opioid dosage values, estimated by linear regression model including dosage by treatment interaction. FST = fentanyl sublingual tablets; SCM = subcutaneous morphine; OMEDD = oral morphine equivalent daily dose; NRS = numerical rating scale.

Table 3
Average Adverse Event Intensity Scores Assessed at 30 and 60 Minutes According to Previous Opioid Exposure and Treatment Group

	Previous Opioid Exposure					
	Low Dosage 20–30 mg ($N = 47$)		Medium Dosage 31–70 mg ($N = 35$)		High Dosage 71–120 mg ($N = 31$)	
Adverse Event	FST	SCM	FST	SCM	FST	SCM
Somnolence						
Mean	0.59	0.90	0.89	0.63	0.90	0.91
SD	0.65	0.72	0.90	0.47	0.63	0.58
Difficulty concentrating						
Mean	0.09	0.25	0.33	0.25	0.23	0.50
SD	0.25	0.53	0.59	0.45	0.42	0.52
Nausea						
Mean	0.13	0.23	0.14	0.09	0.13	0.09
SD	0.31	0.53	0.33	0.27	0.35	0.27
Vomiting						
Mean	0.00	0.13	0.00	0.00	0.00	0.00
SD	0.00	0.45	0.00	0.00	0.00	0.00
Dry mouth						
Mean	0.57	0.72	0.64	0.59	0.47	0.94
SD	0.59	0.77	0.59	0.71	0.64	1.00
Confusion						
Mean	0.00	0.22	0.17	0.13	0.00	0.13
SD	0.00	0.45	0.34	0.29	0.00	0.34
Muscle spasm						
Mean	0.13	0.09	0.11	0.13	0.13	0.09
SD	0.34	0.29	0.32	0.34	0.35	0.27
Stomach ache						
Mean	0.04	0.07	0.11	0.00	0.10	0.22
SD	0.21	0.23	0.47	0.00	0.28	0.48
Difficulty urinating						
Mean	0.02	0.00	0.00	0.00	0.00	0.00
SD	0.10	0.00	0.00	0.00	0.00	0.00
Difficulty breathing						
Mean	0.13	0.04	0.28	0.09	0.00	0.28
SD	0.34	0.21	0.46	0.27	0.00	0.45
Itching						
Mean	0.13	0.04	0.17	0.06	0.00	0.06
SD	0.63	0.21	0.51	0.25	0.00	0.25

FST = fentanyl sublingual tablets; SCM = subcutaneous morphine.

therefore possible to say that the study doses constitute a clinically reasonable choice for the comparison.

Stratified randomization by previous opioid exposure allowed a balanced number of patients receiving either drug among who were exposed to higher or lower chronic opioid dose, and in fact mean daily dose is 54.6 mg OMEDD in the fentanyl group and 54.2 mg in the morphine group.

The comparison of two widely different routes of administration is certainly affected also by the higher degree of variability associated with sublingual versus subcutaneous absorption. In fact, our noninferiority design measured a slight advantage for morphine both in terms of pain relief an of re-medication frequency. Acknowledging these limitations implies that the individual variability in fentanyl bioavailability and previous OMEDD exposure may indeed obscure an effect of tolerance on efficacy. A patient with relative high SLF bioavailability may reach better analgesic effect, in spite of relatively higher opioid tolerance, than a patient for whom SLF bioavailability would be lower, whereas this factor would not be relevant for the patients receiving SCM. This is, however, happening also in clinical practice, and it is therefore relevant also in choosing initial fentanyl doses according to a proportional or titration method.

In this study, patients had been treated chronically with different opioids including morphine, oxycodone, fentanyl, codeine, and tramadol. Incomplete cross tolerance[31] to morphine or fentanyl could make it more difficult to predict and study the relative potency of either SCM or FST in individual cases. However, the study closely reflects the clinical situation, results are therefore still relevant although larger trials would be required to identify specific opioid to opioid interaction in modifying the efficacy of a given opioid rescue dose.

Another limitation of these secondary analyses is the absence of specific prospective sample size calculation and then a potential lack of power in subgroup analyses. However, simple effects and interaction estimates resulted modest in magnitude. This may

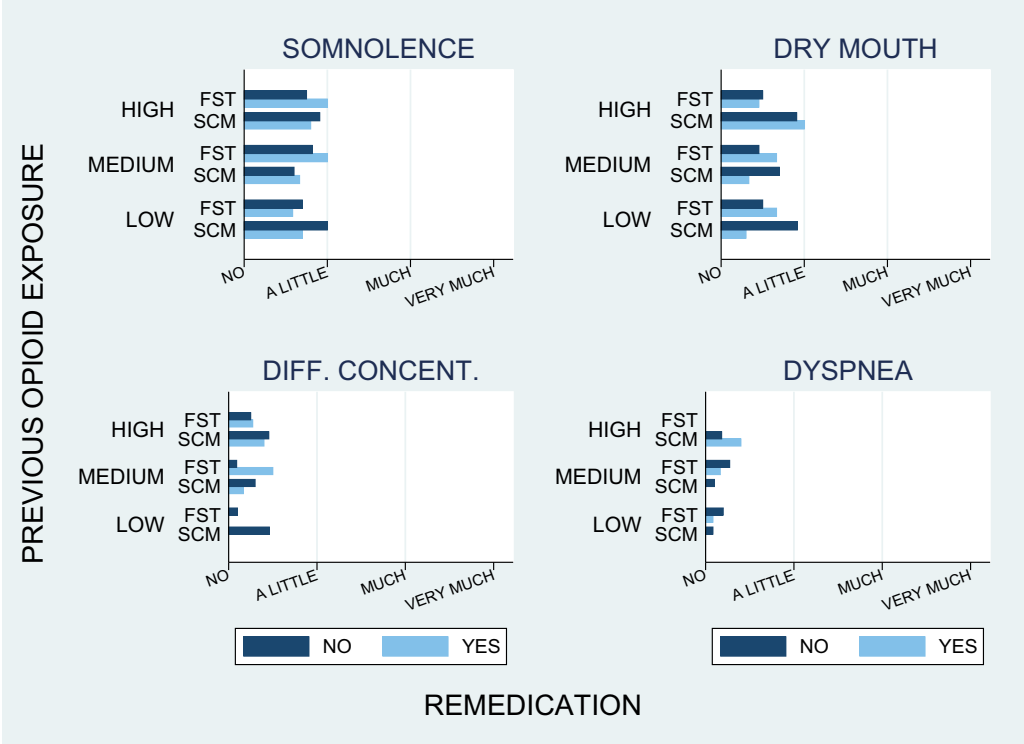

Fig. 3. Intensity of four among the most common opioid-related adverse events at 60 minutes, by treatment (FST and SCM), dosage of previous opioid exposure (low, medium, and high), and re-medication at 30 minutes (no/yes). FST = fentanyl sublingual tablets; SCM = subcutaneous morphine.

suggest that lack of statistical significance is not predominantly because of a lack of power but rather to an actually small effect of baseline opioid exposure on the outcomes examined.

The contribution provided by this study to present knowledge on opioid clinical pharmacology is the evaluation of previous opioid exposure as factor potentially influencing individual variability in the response to FST and SCM. Results indicate a limited clinical impact of opioid exposure in doses from 20 to 120 mg OMEDD on efficacy and tolerability of the two drugs and support clinical practice to start with SCM 5 mg or FST 100 μg and titrate to effect in this group of patients. These results are otherwise compatible with observations suggesting the development of clinically detectable changes because of tolerance with the use of higher opioid doses.[25,26] In practice, the use of 200 μg of SLF has been suggested as a starting dose in patients with a previous OMEDD ≥ 120 mg;[10,25] and in our experience, 51% of patients with previous OMEDD exposure between 20 and 120 mg needed a second 100 μg dose after 30 minutes from the first dose. Therefore, although not recommended by registered prescription rules, it is our practice to start fentanyl transmucosal tablets administration at 200 μg dose in patients who are already taking at least 120 mg OMEDD. This individual practice could be validated only by a parallel double-blind comparison of titration (100 μg + 100 μg after 30 minutes, if needed) versus immediate administration of 200 μg in an adequately powered sample of patients, accounting also for other clinically relevant variables such as the duration of previous opioid exposure.

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