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Association between fentanyl treatment for acute pain in the emergency department and opioid use two weeks after discharge

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ABSTRACT

Background: Analgesia with fentanyl can be associated with hyperalgesia (higher sensitivity to pain) and can contribute to escalating opioid use. Our objective was to assess the relationship between emergency department (ED) acute pain management with fentanyl compared to other opioids, and the quantity of opioids consumed two-week after discharge. We hypothesized that the quantity of opioids consumed would be higher for patients treated with fentanyl compared to those treated with other opioids.

Methods: Patients were selected from two prospective cohorts assessing opioids consumed after ED discharge. Patients ≥18 years treated with an opioid in the ED for an acute pain condition (≤2 weeks) and discharged with an opioid prescription were included. Patients completed a 14-day paper or electronic diary of pain medication use. Quantity of 5 mg morphine equivalent tablets consumed during a 14-day follow-up by patients treated with fentanyl compared to those treated with other opioids during their ED stay were analyzed using a multiple linear regression and propensity scores.

Results: We included 707 patients (mean age ± SD: 50 ± 15 years, 47% women) in this study. During follow-up, patients treated with fentanyl ($N = 91$) during their ED stay consumed a median (IQR) of 5.8 (14) 5 mg morphine equivalent pills compared to 7.0 (14) for those treated with other opioids ($p = 0.05$). Results were similar using propensity score sensitivity analysis. However, after adjusting for confounding variables, ED fentanyl treatment showed a trend, but not a statistically significant association with a decreased opioid consumption during the 14-day follow-up (B = −2.4; 95%CI = −5.3 to 0.4; $p = 0.09$).

Conclusions: Patients treated with fentanyl during ED stay did not consume more opioids after ED discharge, compared to those treated with other opioids. If fentanyl does cause more hyperalgesia compared to other opioids, it does not seem to have a significant impact on opioid consumption after ED discharge.

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1. Introduction

Opioids are frequently used for moderate to severe acute pain in the emergency department (ED) and postsurgical settings. However, treatment of pain with opioids following ED discharge is associated with adverse effects (constipation, nausea/vomiting, dizziness, drowsiness, and weakness) [1], and can also have other unfavorable consequences such as tolerance (higher dose required to preserve pain relief), physical and psychological dependence, addiction, and hyperalgesia [2]. Opioid-induced hyperalgesia (OIH) is a paradoxical phenomenon making patients more sensitive to pain, causing occasional exacerbation of pain sensation rather than pain relief [3]. This includes all conditions where increased pain sensitivity is present: allodynia (pain in response to a non-nociceptive stimulus), decreased pain thresholds, or increased responses to a supra-threshold painful stimulation [4]. This phenomenon is different from opioid tolerance which is the need to increase the dose to maintain analgesic effects. In contrast with OIH, in opioid tolerance, a painful stimulus will not result in an exacerbation of the pain sensation [5].

Numerous animal experimental models have reported OIH [6-9]. The strongest evidence of OIH in humans has been observed in healthy volunteers receiving morphine infusions [3,10]. A systematic review of chronic opioid exposure also demonstrated OIH using thermal noxious stimuli. However, there was no change in pain thresholds or OIH with electrical stimuli [11], and another review found no hyperalgesia in long-term opioid use for chronic pain [12]. A recent systematic review performed in nonsurgical settings identified OIH up to 6.5 h after opioid use, mostly in patients who received fentanyl and remifentanil. However, none of the studies performed an analysis of the effects of OIH on opioid consumption after that period [13]. In post-operative settings, patients treated with a high-dose of fentanyl have shown higher pain scores [14-16], higher morphine use, and hyperalgesia [17-19]. Furthermore, a review of 6 randomized controlled trials evaluated the effect of fentanyl on pain in acute surgical settings. Four of the six trials supported the occurrence of fentanyl-induced hyperalgesia associated with increased opioid consumption [20]. Thus, fentanyl has been associated with hyperalgesia in the acute post-operative context and in healthy volunteers settings, but has not been investigated in an ED population at a dosage used to manage acute pain compared to other types of opioids. Additionally, the impact on pain scores and opioid use after ED discharge has not been well described.

The main objective of this study was to assess the association between fentanyl received to treat acute pain in the ED and the quantity of opioids consumed during a two-week follow-up after discharge. Based on previous results observing fentanyl associated hyperalgesia in short-term controlled settings, we hypothesized that the quantity of opioids consumed would be higher for patients treated with fentanyl for acute pain in the ED, compared to those treated with other opioids.

2. Methods

2.1. Study design and setting

The study population was selected from two patient cohorts gathered with the identical objective of evaluating the quantity of opioids consumed for acute pain complaints after ED discharge. The first cohort was collected for a pilot study whose results were previously published [21] while the second one was collected for a Canadian Institutes of Health Research (CIHR) funded research project (ClinicalTrials.gov: NCT03953534). A patient partner was involved in the design and conduct of the funded study. Both these prospective cohort studies were conducted in the same ED of a tertiary care level 1 trauma academic centre with an affiliated emergency medicine residency program, and an annual census of approximately 65,000 ED visits. This study is a post-hoc analysis of these data. Approval was obtained from the local institutional ethics review board for both studies.

2.2. Participant selection

Patients aged 18 years and older, treated in the ED from June 2016 to July 2017 for the pilot study, and from May 2019 to December 2020 for the CIHR funded study were identified by ED physicians 24/7 and recruited by research nurses. We included patients with an acutely painful condition present for less than two weeks and discharged from the ED with an opioid prescription. We excluded patients who did not speak French or English, were using opioid medications prior to the ED visit, or were suffering from cancer or chronic pain.

2.3. Measurements

Emergency department physicians obtained the patients' consent to be contacted by the research nurses to explain the study. The research nurses subsequently obtained informed consent in person or by phone. Patient demographic information, pain intensity at triage, arrival mode, triage priority, length of stay in the ED, and pain medication received during their ED stay were extracted from the local electronic medical system. Emergency department physicians also entered the final diagnosis, pain intensity at discharge, and which pain medications were prescribed. Pain intensity was evaluated with a verbal 11-point Numerical Rating Scale (NRS) ranging from 0 to 10, where 0 represents 'no pain at all' and 10 represents 'the worst imaginable pain.' Patients also received a 14-day diary in which they recorded the quantity, time, and name of all the pain medication consumed daily. Using pre-addressed and pre-stamped envelopes, these diaries were mailed back after completion. Patients in the CIHR funded study also had the choice of completing an identical online version of the diary. All patients were also interviewed over the phone by a research assistant two weeks post-ED visit, and responded to questions concerning their pain medication use and current pain intensity. Patients were asked if they had filled their opioid prescription; the consumed quantity of opioids, acetaminophen, or nonsteroidal anti-inflammatory drugs (NSAIDs); and whether they had received and filled any new opioid prescriptions in the last two weeks. In the pilot study, intraclass correlation coefficient performed on consumed opioids was 0.72 (95%CI: 0.66–0.77) between the 14-day diaries and phone interviews which is considered good concordance between both measures [22]. Therefore, data from the phone interviews was used for patients with missing 14-day diaries in both cohorts. The two-week follow-up period was chosen because acute pain usually lasts for a short time and most patients stop taking opioids (88% in the pilot study) [23]. Study data was collected and managed using REDCap (Research Electronic Data Capture), a secure, web-based application tool hosted on the hospital server [24].

2.4. Stratification

Because different pain diagnoses have different pain resolution patterns [25], we expected the quantity of opioids required to treat acute pain to vary across pain conditions. The most frequently reported ED pain conditions in the literature, and in the pilot study, were musculoskeletal, fracture, renal colic, and abdominal pain [26]. The pilot data also showed that 85% of patients receiving opioids had one of these four pain conditions [23]. In the CIHR funded study, we also separated the musculoskeletal pain condition into 2 categories (back or neck pain) and other musculoskeletal pain (bruise, sprain, tendinitis, etc.) because back and neck pain tend to last longer. For a more pragmatic approach, we included a group of patients with all other uncategorized pain conditions (e.g., abscess, burn, dental pain). These six pain condition categories served as stratification variables for our main outcome.

2.5. Outcomes

The primary outcome of this study was the quantity of opioid tablets consumed during the two-week follow-up period extracted from the

diary (paper or electronic) or phone interview (if the diary was not completed). The quantity of opioid tablets consumed cannot be summed as it stands due to the different potency and varying dosages across opioids. Thus, opioid prescription and consumption were transformed into 5 mg tablets of morphine equivalent [27,28], using Berdine and Nesbit's [29] method. A dosage of 3.33 mg of oxycodone and 1.25 mg of hydromorphone were considered equipotent to one 5 mg morphine tablet. The main predictor of the study was whether patients were treated for their acute pain with fentanyl (intravenous or intranasal) at any dosage during their ED stay, compared to patients treated with other opioids. The same quantity was determined for each pain condition category.

2.6. Analysis

Comparison of baseline characteristics between patients treated with fentanyl during their ED stay and those treated with another kind of opioid were done with *t*-test, Mann-Whitney *U* tests, and Chi-square tests as appropriate. The quantity of opioid consumed during the two-week follow-up was compared between the two groups using Mann–Whitney U test for the whole sample, and for each of the pain conditions. Multiple linear regression was used to predict opioids used during follow-up, with fentanyl and 'other' opioid group as the main predictor, controlling for age, sex, pain conditions, triage priority, ED arrival mode, quantity of 5 mg morphine equivalent prescribed, and ED treatment section. Pain intensity at triage was initially entered in the regression model (giving similar results) but removed because this information was often missing. The same analyses were repeated for each pain condition. Dummy variables were constructed within pain condition, with the category 'Other' as reference. Linearity, multicollinearity, independence and normality of residuals were tested within multiple linear regression analyses. Alpha level was set at 0.05, and all statistics were performed using SPSS version 26 (IBM, Somers, NY).

As sensitivity analysis, we also used propensity score pair-matching (1:1 ratio) to control for potential selection bias and identify comparable patients. Pre-treatment characteristics for the propensity score model were selected based on baseline characteristic and variables that authors determined could influence treatment selection. The following variables were included in the propensity score: age, sex, pain conditions, triage priority, ED arrival mode, and area in the ED where the patient was treated. We gave priority to exact propensity score matching, for those with non-exact matching we used a caliper of 0.2 (proportion of the standard deviation of the logit of the propensity score) without replacement method [30]. This strategy yields a good balance between close matching and loss of experimental patients. Results of the matching on confounders will be presented as standardized mean difference. Wilcoxon signed rank paired test was finally used to compare the quantity of opioids used during follow-up by fentanyl (versus other opioids) on this propensity score matching sample.

The study sample size was estimated based on the main multiple linear regression analysis. Controlling for 3 confounding variables, that explained an estimate of 10% of the variance in the opioids used up until the follow-up, our cohort of 707 patients could detect 1% of variance explained by the fentanyl group variable, and achieve a power of 0.80, with an alpha level of 0.05 (PASS version 11.0; NCSS, LLC. Kaysville, Utah).

3. Results

3.1. Study cohort description

A total of 1369 patients meeting the initial study inclusion/exclusion criteria were contacted. Of these, 26% refused to participate, 25% were not treated with an opioid within the ED, and 13% could not be reached for the 14-day follow-up, leaving 707 participants (Fig. 1). Patients' mean age was 50 (±15) years, 47% were female, and the median NRS pain intensity at triage was 8, decreasing to 4 at ED discharge. Patients treated in the ED with fentanyl received a median of 62.5 μg (IQR = 50–100) during their ED stay and baseline characteristics compared to those treated with other opioids were different (Table 1). Patients treated with fentanyl (13% of the cohort) were more often: women, arrived by ambulance and were put on a stretcher, had a higher triage level priority, had more fractures, and had higher NRS triage pain, but also had lower NRS pain at discharge, had less back and neck pain, and had a lower quantity of 5 mg morphine equivalent pills prescribed at discharge. Patients of the "other opioid" category were treated during their ED stay with morphine (57%), oxycodone (27%), and hydromorphone (16%).

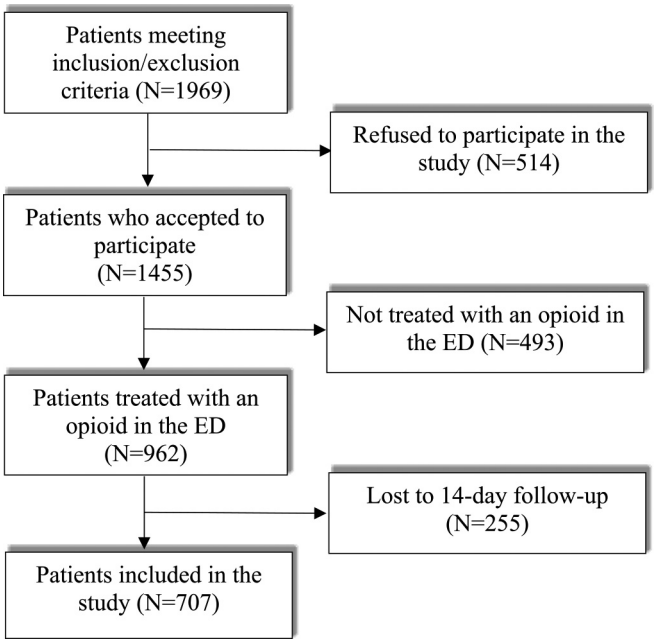

Fig. 1. Flow chart of patients' enrollment in the study.

The results of the propensity score matching on baseline characteristics are also presented in Table 1. Two patients treated with fentanyl could not be paired using our matching strategy, leaving a sample of 89 patients in each group. Both groups are now more similar on the confounding variables as the standardized mean difference are generally low.

3.2. Main results

In univariate analysis, patients treated with fentanyl (compared to other opioids) in the ED consumed statistically less opioids after discharge (1.2 pills of 5 mg morphine or equivalent, $p = 0.05$) (Table 2). In the subgroup analysis of pain condition categories, the "other musculoskeletal" category seemed to account for much of the difference between the groups (9 pills of 5 mg morphine or equivalent, $p < 0.001$). This "other musculoskeletal" pain condition was composed of bruises (48%), strains (30%), tendinitis (10%), bursitis (8%), and tears (4%).

Results of the multiple linear regressions are presented in Table 3. Assumptions of linear regression were tested and fulfilled. Controlling for confounding variables, patients treated with fentanyl during their ED stay showed a trend, but not a statistically significant association with a decreased opioid consumption at the two-week follow-up (−2.4 pills of 5 mg morphine or equivalent, $p = 0.09$). The main confounding variables that reduced the negative univariate association observed between fentanyl and opioid used were the type of painful condition and the difference in the quantity of opioid prescribed at ED discharge.

Table 1
Comparisons of baseline characteristics between patients treated with fentanyl during their emergency department stay and those treated with other types of opioid.

Baseline characteristics	Original sample		Sample adjusted for propensity score matching		
	Fentanyl (N = 91)	Other opioid (N = 616)	Fentanyl (N = 89)	Other opioid (N = 89)	SMD
Mean age (±SD)	47.2 (16.9)	50.6 (15.0)	47.6 (16.9)	47.6 (15.4)	0
Sex: Female (%)	59.3	45.6*	59.6	52.8	0.14
ED arrival mode (%)					
-By themselves	64.8	80.0*	66.3	77.5	0.25
-By ambulance	35.2	20.0	33.7	22.5	
High triage priority (level 1 or 2) (%)	62.6	51.1*	61.8	61.8	0
Median (±IQR) pain intensity (0–10 scale) at triage	9 (2)	8 (3)*	9 (2)	8 (2)	
ED treatment section (%)					
-Ambulatory	38.5*	53.1	39.3	33.7	0.12
-On stretcher	61.5	46.9	60.7	66.3	
Type of pain conditions (%)					
-Back and neck pain	12.1	25.3*	12.4	4.5	0.29
-Other musculoskeletal	16.5	17.7	16.9	13.5	0.09
-Fracture	30.8	14.6	29.2	25.8	0.08
-Renal colic	24.2	25.5	24.7	34.8	0.22
-Abdominal pain	1.1	5.4	1.1	0	0.15
-Other	15.4	11.5	15.7	21.3	0.14
Received acetaminophen during ED stay (%)	50.5	51.6	51.7	43.8	
Received NSAIDs during ED stay (%)	40.7	40.4	40.4	41.6	
Acetaminophen prescription at ED discharge (%)	65.9	64.9	66.3	68.2	
NSAIDs prescription at ED discharge (%)	48.4	49.4	48.3	48.9	
Opioid prescription type at discharge (%)					
-Morphine	41.8	47.2*	40.4	54.5	
-Oxycodone	23.1	30.9	23.6	23.9	
-Hydromorphone	35.2	22.0	36.0	21.6	
Median (IQR) morphine 5 mg equivalent tablets prescription	20 (18)	30 (24)*	20 (18)	30 (28)	
Median (IQR) ED stay (hours)	6 (4)	6 (4)	7 (4)	7 (6)	
Median (±IQR) pain intensity (0–10 scale) at ED discharge	3 (4)	4 (5)*	3 (4)	4 (6)	

IQR: interquartile range; SD: standard deviation; NSAIDs: nonsteroidal anti-inflammatory drug; ED: emergency department; SMD: standardized mean difference for variables used in the propensity score matching; *$p < 0.05$.

3.3. Sensitivity analysis

For the propensity score matching sample, patients treated with fentanyl ($N = 89$) during their ED stay were still associated with decreased opioid consumption at the two-week follow-up (fentanyl: median = 5.6 (IQR = 0–14); other opioids: median = 7 (IQR = 2–17); $p = 0.03$).

Table 2
Univariate comparison of quantity of opioid consumed (5 mg morphine equivalent pills) two-week after emergency department discharge between patients treated with fentanyl and those treated with other types of opioid during their emergency department stay.

Pain conditions	Fentanyl exposure	Other opioid exposure	p from Mann-Whitney tests
	Median MME (IQR)	Median MME (IQR)	
Total sample	5.8 (0–14) $n = 88$	7.0 (2–16) $n = 609$	0.05
Back and neck pain	6.0 (4–12) $n = 9$	9.0 (4–18) $n = 154$	0.38
Other musculoskeletal	1.0 (0–9) $n = 15$	10.0 (3−22) $n = 109$	0.001
Fracture	13.0 (3−20) $n = 27$	12.0 (4–30) $n = 88$	0.67
Renal colic	4.2 (0−13) $n = 22$	2.0 (0–9) $n = 154$	0.63
Abdominal pain[2]	- ($n = 1$)	- ($n = 33$)	–
Other pain condition	2.4 (0–9) $n = 14$	6.0 (2–14) $n = 71$	0.05

IQR: interquartile range; MME: 5 mg Morphine Equivalent pills used during the two-week follow-up; [2]: not enough fentanyl cases to perform statistical test.

4. Discussion

Contrary to our hypothesis, this study showed, after controlling for confounding variables, that fentanyl use in the ED showed a trend, but not a statistically significant association with less opioid consumption during the two weeks after ED visit for acute pain (−2.4 pills of 5 mg morphine or equivalent). Results from the propensity score sensitivity analysis showed a similar difference (−1.4 pills of 5 mg morphine or equivalent) in opioid consumption. However, these differences in the quantity of opioids consumed during these two weeks were not clinically significant. The main confounding variables seemed to be the type of painful condition and the quantity of opioid prescribed at discharge. It has been previously shown that certain type of painful condition like fracture [21] and a higher quantity of opioids prescribed at discharge were associated with higher opioid consumption at home [31].

Various factors can explain our results; after fentanyl use, hyperalgesia has been reported up to 6.5 h after exposure in non-surgical setting, after surgery, increased consumption of opioids up to 23 h and increase pain intensity up to 72 h [13,18,32]. Therefore, it is possible that these effects fades after this time without new exposure to fentanyl. Furthermore, hyperalgesia has been reported mostly at higher doses of fentanyl (i.e.: 3 to 70 μg/kg) not usually used in the ED setting (median total of 62.5 μg per patient in our study), so hyperalgesia may not be present at lower doses [15,16,32]. Hyperalgesia could also be caused by opioids other than fentanyl consumed during ED stay and/or the two weeks until follow-up [33].

Even if we controlled for the type of painful condition, the different pain trajectories after ED discharge associated with specific conditions could lead to different quantities of opioid consumption [34]. For

Table 3
Results of multiple linear regressions predicting the quantity of opioid consumed (5 mg morphine equivalent pills) during the two-week follow-up.

Pain condition/predictors	B	SE	95% CI (B)	*p*-value
Total sample				
Fentanyl	−2.4	1.5	−5.3 to 0.4	0.09
Age	0.01	0.03	−0.05 to 0.07	0.68
Sex (Female)	−1.0	0.98	−2.9 to 0.9	0.30
Triage priority (High)	1.1	1.1	−1.0 to 3.2	0.30
ED arrival mode (by ambulance)	1.5	1.3	−1.0 to 4.0	0.24
ED treatment section (on stretcher)	−0.09	1.2	−2.5 to 2.3	0.94
Morphine 5 mg equivalent pills prescribed	0.2	0.02	0.15 to 0.23	0.001
Pain condition:				
Back and neck pain	2.3	1.7	−1.0 to 5.6	0.18
Other musculoskeletal	3.0	1.8	−0.5 to 6.5	0.09
Fracture	4.9	1.8	1.3 to 8.5	0.008
Renal colic	−4.5	1.8	−9.4 to −0.9	0.02
Abdominal	−4.2	2.6	−9.4 to 0.9	0.10
Other (reference)	-	-	-	-
Back and neck pain				
Fentanyl	−5.9	4.7	−15.2 to 3.4	0.21
Age	0.06	0.08	−0.1 to 0.2	0.48
Sex (Female)	−2.6	2.2	−7.0 to 1.8	0.25
Triage priority (High)	2.7	2.3	−2.0 to 7.3	0.26
ED arrival mode (by ambulance)	1.2	3.0	−4.8 to 7.2	0.70
ED treatment section (on stretcher)	1.1	2.7	−4.1 to 6.4	0.67
Morphine 5 mg equivalent pills prescribed	0.1	0.06	0.01 to 0.24	0.03
Other musculoskeletal				
Fentanyl	−5.7	4.1	−13.8 to 2.4	0.17
Age	0.1	0.08	−0.03 to 0.3	0.11
Sex (Female)	−5.5	2.6	−10.6 to −0.5	0.03
Triage priority (High)	1.2	2.7	−4.1 to 6.6	0.65
ED arrival mode (by ambulance)	4.0	3.3	−2.4 to 10.5	0.22
ED treatment section (on stretcher)	−2.7	3.3	−9.2 to 3.9	0.42
Morphine 5 mg equivalent pills prescribed	0.2	0.05	0.1 to 0.3	0.001
Fracture				
Fentanyl	−3.7	3.5	−10.6 to 3.1	0.28
Age	−0.2	0.1	−0.4 to −0.02	0.03
Sex (Female)	6.7	2.8	1.1 to 12.4	0.02
Triage priority (High)	2.1	2.9	−3.6 to 7.8	0.46
ED arrival mode (by ambulance)	2.6	3.7	−4.7 to 9.9	0.49
ED treatment section (on stretcher)	6.8	4.0	−1.1 to 14.8	0.09
Morphine 5 mg equivalent pills prescribed	0.2	0.04	0.2 to 0.3	0.001
Renal colic				
Fentanyl	2.5	2.1	−1.7 to 6.7	0.24
Age	−0.01	0.06	−0.1 to 0.1	0.89
Sex (Female)	1.1	1.5	−2.0 to 4.1	0.48
Triage priority (High)	−2.0	2.1	−6.2 to 2.1	0.33
ED arrival mode (by ambulance)	−3.9	2.1	−8.1 to 0.2	0.06
ED treatment section (on stretcher)	−0.8	2.5	−5.7 to 4.1	0.76
Morphine 5 mg equivalent pills prescribed	0.1	0.04	0.05 to 0.2	0.001
Abdominal pain[1]	–	–	–	–
Other pain condition				
Fentanyl	−2.5	2.7	−7.8 to 2.9	0.36
Age	−0.05	0.06	−0.2 to 0.08	0.47
Sex (Female)	−3.9	2.0	−7.9 to 0.02	0.05
Triage priority (High)	−2.0	2.2	−6.3 to 2.4	0.38
ED arrival mode (by ambulance)	5.4	3.0	−0.6 to 11.5	0.08
ED treatment section (on stretcher)	−3.8	2.4	−8.6 to 1.0	0.12
Morphine 5 mg equivalent pills prescribed	0.3	0.07	0.2 to 0.5	0.001

B: Unstandardized regression coefficient; SE: Standard error of B; 95% CI: 95% confidence intervals; ED: emergency department; [1]: not enough fentanyl cases to perform statistical test.

example, musculoskeletal pain was associated with a very different pain evolution, from severe pain during two weeks, to then having the severe initial pain diminish to mild or no pain at two weeks [34]. Also, patients could follow the World Health Organisation analgesic ladder or be afraid of a substance use disorder and not consume opioids except for severe pain, and hyperalgesia may not impact the presence of severe pain. Furthermore, hyperalgesia has been demonstrated mostly in the presence of a new painful stimulus, and it may not impact the initial pain condition in the same fashion and still produce significant pain relief. For example, in a study of a four-week follow-up, the presence of OIH was demonstrated in patient with chronic radicular pain; OIH was more prevalent as opioid dosage increased but also showed a significant reduction in daily pain scores and decrease in pain-induced disability as dosage increased. Possible clinical OIH was present in 4 patients (13%) and could also be explained by worsening of clinical condition [33]. This result can support the hypothesis that the presence of hyperalgesia may not necessarily influence pain relief for the initial pain condition.

It is also possible that confounding factors associated with the use of fentanyl, rather than another opioid, may also have an impact on pain outcomes and subsequent opioid use. For example, fentanyl is often used as an analgesic for procedures in certain painful conditions such as the reduction of displaced fractures and dislocations because of its rapid onset of action. It is reasonable to believe that in these settings, the procedure itself will impact pain resolution and opioid use, rather than the use of fentanyl. However, the argument could be made that a displaced fracture should generate more pain after discharge from the

ED, even after reduction, than a non-displaced fracture. Furthermore, our sensitivity analysis with paired propensity scores did demonstrate that fentanyl treated ED patients consumed statistically less opioids after discharge.

Tolerance, defined as an increased dose of an opioid to achieve the same analgesic effect, can be offset by increasing opioid dose. In contrast, hyperalgesia is usually made worse by increasing the opioid dosage. However, the clinical presentation of escalating opioid dosage for either phenomenon is the same and is difficult to distinguish without specific testing for allodynia (pain in response to a non-nociceptive stimulus), decreased pain thresholds, or increased responses to a supra-threshold painful stimulation. If fentanyl hyperalgesia persisted days after administration and other opioids caused less hyperalgesia, the varying prevalence of tolerance in the study cohort could also explain the lack of effect on the quantity of opioid consumed [2]. Randomized prospective studies on the use of fentanyl and other opioids in the ED with specific testing for hyperalgesia during follow-up are needed to clarify their impact after ED discharge.

5. Limitations

This study has limitations; since the design of the study was observational, there was no randomization of fentanyl treatment and no standardization of the quantity of opioids prescribed at ED discharge, generating some possible selection bias. It was done at a single site, urban, academic, tertiary care hospital, and thus findings may not be generalizable to other healthcare settings. This study was not designed to directly measure opioid hyperalgesia during the two-week follow-up.

6. Conclusions

In summary, patients treated with fentanyl compared to those treated with other opioids during their ED stay did not consume more opioids after ED discharge. If fentanyl does cause more hyperalgesia compared to other opioids, it does not seem to have a significant impact on opioid consumption after ED discharge.

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Author contributions

R.D. J.P. JM.C. D.W. and A.C. conceived the study and obtained research funding. All authors contributed to the final protocol and data interpretation. J.P. was responsible for data management and statistical analyses. R.D. drafted the manuscript, and all authors contributed substantially to its revision. All authors approved the final manuscript as submitted and have agreed to be accountable for all aspects of the work.

Data sharing statement

Original data.

Declaration of Competing Interest

There is no financial benefit or conflict of interest to report from all co-authors.

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