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Quantity of opioids consumed following an emergency department visit for acute pain: a prospective cohort study.

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Running head: Opioid use after an ED visit for acute pain

ABSTRACT

Objectives: Some suggest that prescription opioid diversion is a significant contributor to the opioid misuse epidemic. We examined the quantity of opioids consumed by emergency department (ED) discharged patients after treatment for an acute pain condition, and the percentage of unused opioids available for potential misuse.

Design: Prospective cohort study.

Setting: Tertiary care trauma centre academic hospital.

Participants: A convenience sample of patients aged 18 years and older who visited the ED for an acute pain condition (≤ 2 weeks) and were discharged with an opioid prescription. Patients completed a 14-day paper diary in which they list their daily pain medication use. To reduce lost to follow-up, two weeks post-ED visit, participants also responded to phone interview questions about their previous 14-day pain medication use.

Outcomes: Quantity of morphine 5 mg equivalent pills prescribed, consumed, and unused during a 14-day follow-up. Quantity of opioids to adequately supply 80% of patients was also calculated.

Results: Results for 627 patients were analyzed (mean age ±SD: 51±16 years, 48% women). Patients consumed a median of 7 morphine 5 mg equivalent (M5E) pills (Q1-Q3: 2–17). They were discharged from the ED with a median prescription of 30 M5E pills (Q1-Q3: 20–48), and 95% filled their prescription. For the whole sample, 32% of the total prescribed opioids were consumed, with 68% remaining unused. The quantity of opioids to adequately supply 80% of patients was 20 M5E pills.

Conclusions: Patients with an acute pain condition at ED discharge consumed less than 10 M5E pills in the following two weeks, leaving two-thirds of the prescription available for misuse. ED physicians should adapt their prescription practice to minimize unused opioids.

STRENGTHS AND LIMITATIONS OF THIS STUDY

-First study to document opioids consumption after an acute pain emergency department visit.

-Use of a 14-day diary to document opioid consumption.

-Self-reported phone interview data was validated with the 14-day diary information.

-The convenience sample from one ED centre and the small sample size for less frequent pain conditions limit the generalization of our results.

INTRODUCTION

In the 1990s, physicians, who were perceived as undertreating pain, changed their practice in order to identify and treat pain more effectively.[1] Consequently, emergency department (ED) opioid prescriptions increased significantly in the last two decades.[2 3] Meanwhile, opioid misuse (i.e., intentional use for nonmedical purposes), dependence, overdoses, and deaths have increased to epidemic proportions in both the US and Canada.[4-12]

Over 10 million Americans have misused opioids at some point in their life.[13] It is becoming increasingly clear that the availability of unused prescription opioids contributes to misuse.[14] For example, 71% of opioid abusers received them through the diversion of prescription opioids (i.e., transfer of opioids to someone other than the initial prescription holder), and in 55% of cases, these pills were the unused medications of friends or family members.[13 15]

Some US cities and states have formulated ED opioid prescribing guidelines[16 17] and developed prescription drug monitoring programs in hopes of preventing opioid abuse and deaths.[18] These recommendations can be summarized as follows: limit the prescription to a three-day supply (30 pills maximum), avoid prescribing long-acting opioids, and avoid refilling lost or stolen prescriptions.[19] However, these guidelines were not based on prospectively collected data, and possibly neglected patient-centered outcomes such as quantity of opioid needed for pain relief.

Prospective surgical studies have shown wide variation in the number of opioid pills prescribed for the same surgical procedure. Moreover, 58% to 92% of the prescribed opioids were unused,[14 20-22] and the majority (91%) were not properly stored or discarded,[20] leaving them accessible for potential misuse.[23] Studies on ED opioid prescriptions draw their data from large retrospective[24 25] administrative databases, and therefore cannot distinguish between acute and chronic pain in their patient populations. In addition, they are unable to determine whether or not (and how many) opioids were actually consumed.

The main objective of this study was to determine the quantity of opioids consumed by ED-patients discharged with an acute pain condition. Based on our pilot study,[27] we hypothesized that the quantity of opioids that was consumed during the two weeks following an ED visit for acute pain would be fewer than 10 pills of oral morphine 5 mg equivalent.

METHODS

Study design and setting

This prospective cohort study was conducted in the ED of a tertiary care level 1 trauma centre academic hospital with an affiliated emergency medicine residency program and an annual census of approximately 65,000 ED visits (mostly adults). Approval was obtained from the local institutional ethics review board. Patients were informed that results of the study could be published and accessible upon request.

Selection of participants

Patients aged 18 years and older and treated in the ED from June 2016 to July 2017 were recruited 24/7. We included patients with an acute pain condition present for less than two weeks and discharged from ED with an opioid prescription. Patients with an opioid prescription were identified by ED physicians and then recruited by research nurses. A convenience sample was used because we were not able to determine the number of patients missed by ED physicians. We excluded patients who did not speak French or English, were using opioid medication prior to the ED visit, stayed in the ED > 48 hours, or were suffering from cancer or chronic pain.

Measurements

ED physicians obtained patients' consent to be contacted by the research nurses to explain the study. The research nurses subsequently obtained informed consent. Patient demographic information, pain intensity at triage, arrival mode, triage priority, and length of ED stay were extracted from our computerized medical system. ED physicians entered the final diagnosis, pain intensity at discharge, and

which pain medications were prescribed. Patients also received a 14-day diary in which the patient recorded the quantity, the time and the name of all the pain medication consumed. Partly because of the low percentage of the diary returned in our pilot study, two weeks post-ED visit, patients responded to five brief questions over the phone concerning their pain medication use and current pain intensity. Patients were asked if they had filled their opioid prescription; the quantity of opioids, acetaminophen, or nonsteroidal anti-inflammatory drugs (NSAIDs) they had consumed; and whether they had received and filled any new opioid prescriptions in the last two weeks. Patients were asked to report their pain on a verbal 11-point numerical rating scale (NRS) ranging from 0 to 10, where 0 represents "no pain at all" and 10 represent "the worst imaginable pain." The two-week follow-up period was chosen because acute pain usually lasts for a short time (days or a few weeks), during which most patients stop taking opioids (88% in our pilot study).[26] Study data were collected and managed using REDCap (Research Electronic Data Capture), a secure, web-based application tool hosted in the hospital.[27]

Outcomes

The main outcome of this study was the quantity of opioid pills consumed during the two-week follow-up period extracted from the paper diary or phone interview (if the diary was not returned). The quantity of opioid pills cannot be summed as it stands, due to the different potency of different opioids. In addition, dosages vary across opioid types. In order to compare the different opioid forms, each opioid prescription and consumption was transformed into an oral morphine 5 mg pill equivalent[28 29] (M5E), using Berdine and Nesbit's[30] method. A dosage of 3.33 mg of oxycodone and 1.25 mg of hydromorphone were considered equipotent to one M5E pill. The second outcome was the percentage of prescribed opioid pills that were unused after the two-week follow-up. The third outcome was determined as the number of M5E pills that would adequately supply 80% of patients. Although not supported by any consensus, the 80% threshold was used in a recent surgical study by Hill[14] and could provide a reasonable balance between sufficient pain treatments for a large majority of patients while

limiting the quantity of unused opioids. To facilitate application of the optimal prescription quantities in a clinical setting, each patient's M5E pill consumption was grouped into five-pill bins (0=0; 1 to 5=5, 6 to 10=10; up to a maximum number of M5E pills) before threshold calculations.

Because different pain diagnoses have different pain resolution patterns,[31] we expected the quantity of opioids required to treat acute pain to vary across pain conditions. The most frequently reported pain conditions encountered in the ED are musculoskeletal, fracture, renal colic, and abdominal pain.[25] Our pilot data from HSCM show that 85% of patients receiving opioids had one of these four pain conditions.[26] For a more pragmatic approach, we included a group of patients with all other previously undefined pain conditions (e.g., abscess, burn, tooth pain). These five pain condition categories served as stratification variables for our main outcomes.

Analysis

The study sample size was estimated based on our pilot study, where we observed a consumption of 8.8 opioid pills (SD=10) during a two-week follow-up.[26] To detect a significant difference from the null hypothesis (<10) using a Wilcoxon test assuming non-parametric distribution, we had to recruit at least 499 patients to achieve a power of at least 0.80 with an alpha of 0.05, and we estimated that this would take one year to complete (PASS version 11.0; NCSS, LLC. Kaysville, Utah).

The concordance between the 14-day diary and phone interview on the quantity of M5E pills consumed was assessed with intraclass correlation coefficient. The quantity of consumed pain medication is presented as a median with first and third quartiles (Q1, Q3), since it was not normally distributed. Mann–Whitney U tests were used to assess the effect of sex and age (<65 vs ≥65) on the quantity of M5E pills consumed. Wilcoxon signed rank tests were performed to compare the quantity of consumed M5E pills to the null hypothesis (<10 pills). The Kruskal–Wallis test was used to compare the quantity of consumed M5E pills across pain conditions. Two-by-two comparisons of the quantity of consumed M5E pills across pain conditions were made using Mann–Whitney U tests with Bonferroni

correction for multiple testing. Finally, one-way anova with Tukey-b post-hoc comparisons tests was used to compare the percentage of unused opioids across pain conditions. Alpha level was set at 0.05, and all statistics were performed using SPSS version 23 (IBM, Somers, NY).

RESULTS

During our one-year recruitment period, a total of 1315 patients meeting the inclusion criteria were initially contacted. Of these, 29% had exclusion criteria, 13% declined to participate, and 10% could not be reached for the 14-day follow-up, leaving 627 participants (Figure 1). Non-participating and included patients were similar on all baseline characteristics (Table 1). Patients' mean age was 51 (±16) years, 48% were female, and mean pain intensity at triage was 7.8, decreasing to 4.8 at ED discharge. Intraclass correlation coefficient performed on opioids consumed was 0.72 (95%CI: 0.66-0.77) between the 14-day diary and phone interview which is considered good concordance between both measures.[32] Furthermore, the median number of M5E pills consumed was the same (6.7) for both phone interview and the 14-day diary. Therefore, data from phone interview was used for patients with missing the 14-day diary.

Almost all patients filled their opioid prescription during the two-week follow-up period (95%). The median quantity of prescribed M5E pills was 30 (Q1–Q3: 20–48), and similar across all pain condition categories, varying from 24 to 34 M5E pills (Table 2). Variability in the consumed pain medication for the "other" pain condition category was similar to that for the four more common pain condition categories, suggesting that this patient group is comparable. The median quantity of consumed M5E pills was low (7, Q1–Q3: 2–17) compared to the prescribed quantity, and differed significantly from the null hypothesis (H0:<10; $p<0.001$). The consumed quantity varied significantly across pain condition categories: from 3 M5E pills for renal colic to 11 M5E pills for fracture ($p<0.001$). Multiple comparisons showed that patients suffering from renal colic and abdominal pain consumed fewer opioids than those suffering from musculoskeletal pain or fracture (all $p<0.05$). There

was no significant effect of age (<65 vs ≥65) or sex on the quantity of consumed opioids during the two-week follow-up (p>0.40 for both). Of the whole sample, 79% consumed opioids, 68% used acetaminophen, and 45% used NSAIDs.

Over the course of this study, patients discharged from the ED were prescribed 23,402 M5E pills, of which 7,353 were consumed during the two-week follow-up period, leaving a total of 16,049 (68%) unused M5E pills. The percentage of unused opioids showed significant differences across pain conditions (p<0.01): renal colic (81%) and abdominal pain (78%) patients had a significant higher percentage of unused opioids than patients suffering from musculoskeletal, fracture, or "other" pain condition (62% when averaging the 3 categories; Figure 2).

Patients' pain intensity at two weeks was low (2.0 average) across all pain conditions. Only a minority of patients (<7%) filled a supplemental opioid prescription, indicating that the initial prescriptions were sufficient to treat pain for 93% of patients during the two-week period. The quantity of M5E pills to prescribe in order to adequately supply 80% of all the patients was 20. Patients suffering from renal colic or abdominal pain required only half the quantity compared to patients suffering from fractures (Figure 3).

DISCUSSION

This prospective study showed that patients discharged from the ED with an acute pain condition consumed a median of only 7 M5E pills but received a median of 30 M5E pills prescription, leaving two-thirds of the opioids unused and available for misuse. Furthermore, patients with renal colic or abdominal pain tended to consume fewer opioids during the two-week follow-up compared to patients with musculoskeletal pain or fractures. We also determined that 20 M5E pills could adequately supply 80% of patients while limiting the quantity of unused opioids.

The number of opioids prescribed to patients discharged from the ED with a pain condition in this study was similar to that reported for patients who had upper extremity surgery,[21] common general surgical procedures,[14] and urological surgery.[20] This one-size-fits-all approach, which does not take into account the patient's individual condition, can probably be attributed to the lack of clinical data on opioid consumption.[16 17] During the two-week follow-up, our 68% of opioids left unused is also within the range of percentages observed in surgical studies (58–92%).[14 20-22]. The purpose of this over-prescribing may be to offset the inconvenience, for both patient and physician, of return visits to the ED or another medical service to obtain another prescription.[14] However, these large quantities of unused opioids can be diverted to family and friends, resulting in misuse, dependence, and possibly death by overdose.[20]

Patients suffering from renal colic and abdominal pain needed fewer opioids than those suffering from a fracture or musculoskeletal pain. Rodgers et al. also reported differences in opioid consumption between different types of surgery, finding that bone surgery required more opioids than soft tissue procedures.[21] Furthermore, renal colic shows a unique pain resolution pattern: episodic intense pain until the stone is expelled. These results underscore the need for practitioners to adjust their opioid prescriptions to the type of pain condition. If patients in our study were prescribed opioids in order to adequately supply 80% of the patients (20 M5E pills), a total of 10,492 (45%) pills would not have been available for potential misuse. Since 7 M5E pills (median consumed) would adequately supply 50% of patients, another way of limiting the quantity of unused opioids would require the pharmacist to divide the opioid prescription into portions. Even if repeatable opioid prescriptions are not allowed in most settings, physicians can prescribe a fixed quantity of opioids while instructing the pharmacist to only supply a fraction at a time. For example a physician could prescribe 20 M5E pills and ask the pharmacist to supply only 10 pills at a time with an expiration date of the prescription in two weeks.

This trial has certain limitations. The convenience sample from one ED centre and the small sample size for less frequent pain conditions (especially abdominal pain) limit the generalization of our results. However, patients were recruited 24/7, and consecutive recruitment was limited only by the fact that the investigators could not determine the number of patients missed by ED physicians, it also would be surprising if patients consume opioids differently in other settings. Moreover, the reasons for the participants to stop consuming opioids were not recorded. Some patients may have restricted their opioid use due to adverse effects, fear of addiction, or fear of running out of pills, among others. There is a need for a multi-centre prospective study with larger sample sizes for each pain condition, to determine the impacts on the quantity of unused opioids and incidences of misuse, dependence, and opioid overdose.

In summary, patients who are discharged from the ED with an acute pain condition consumed a median of fewer than 10 morphine 5 mg equivalent pills during the following two weeks, accounting for only one-third of the prescribed opioids, leaving two-thirds of the opioids unused and available for potential misuse. ED physicians should adapt their prescription practice to minimize unused opioids.

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Figure legends

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

Figure 2. Percentage of morphine 5 mg equivalent pills that remained unused after the two-week follow-up for each pain condition category. Mean ± sem are reported. Brackets indicate the results of the Tukey-b multiple comparisons tests. Renal colic and abdominal pain have higher percentage of unused opioids than each of the three other pain conditions.

Figure 3. Number of morphine 5 mg equivalent pills to prescribe to supply 80% of patients for each pain condition category.

Table 1. Comparison of baseline characteristics between included and excluded (refused to participate or were lost to the 14-day follow-up) patients.

Baseline characteristics	Included (N=627)	Excluded (N=310)
Mean age (±SD)	51.0 (15.9)	50.0 (17.8)
Female (%)	47.8	49.0
ED arrival mode (%)		
-By himself	78.6	79.9
-By ambulance	21.3	20.1
High (level 1 or 2) triage priority (%)	42.6	45.3
Mean pain intensity (0-10 scale) at triage (±SD)	7.8 (2.0)	8.0 (1.7)
ED treatment section (%)		
-Ambulatory	64.6	64.1
-On stretcher	35.4	35.9
Type of pain conditions (%)		
-Musculoskeletal pain	44.0	40.3
-Fracture	19.1	19.7
-Renal colic	17.0	17.7
-Abdominal pain	6.0	5.2
-Other	13.9	17.1
Received a Tylenol prescription at ED discharged (%)	71.6	70.3
Received a NSAIDs prescription at ED discharged (%)	45.8	47.4
Opioid prescription type (%)		
-Morphine	43.6	42.7
-Oxycodone	40.5	36.9
-Hydromorphone	15.9	20.4
Median (Q1-Q3) morphine 5 mg equivalent pills prescription	30 (20-48)	30 (20-45)
Median (Q1-Q3) ED stay (hours)	5.3 (3.6-7.7)	5.2 (3.7-7.9)
Mean (±SD) pain intensity (0-10 scale) at ED discharge	4.8 (2.9)	4.7 (2.9)

Q1-Q3: first and third quartile; NSAIDs: nonsteroidal anti-inflammatory drug

Table 2. Pain intensity and pain medication for each pain condition during the two-week follow-up.

Variables	Musculo-squeletal	Fracture	Renal colic	Abdominal	Other	Total
Number of patients	280	119	106	37	85	627
Mean (±SD) pain intensity at ED discharged	5.6 (2.4)	5.2 (2.6)	1.9 (2.7)	3.7 (3.2)	5.5 (3.0)	4.8 (2.9)
Mean (±SD) pain intensity at two-week	2.6 (2.7)	2.6 (2.9)	0.5 (1.2)	1.6 (2.8)	1.8 (2.6)	2.0 (2.6)
Filled opioid prescription (%)	95.1	90.4	99.0	97.1	91.4	94.5
Patients who filled another opioid prescription (n, %)	22 (7.9)	10 (8.4)	3 (2.8)	2 (5.4)	5 (5.9)	42 (6.7)
Median (Q1-Q3) number of M5E prescribed	30 (20-48)	34 (30-60)	31 (23-48)	30 (17-36)	24 (16-42)	30 (20-48)
Median (Q1-Q3) number of M5E consumed	8 (3-20)	11 (3-23)	3 (0-10)	3 (1-9)	6 (2-16)	7 (2-17)
Received acetaminophen prescription at discharged (%)	78.2	79.0	57.5	56.8	63.5	71.6
Consumed acetaminophen (%)	73.9	87.4	49.1	48.6	52.9	67.9
Received NSAIDs prescription at discharged (%)	49.3	28.6	64.2	40.5	37.6	45.8
Consumed NSAIDs (%)	51.8	35.3	50.9	35.1	34.1	45.1

Q1-Q3: first and third quartile; M5E: 5 mg morphine pills equivalent; NSAIDs: nonsteroidal anti-inflammatory drugs

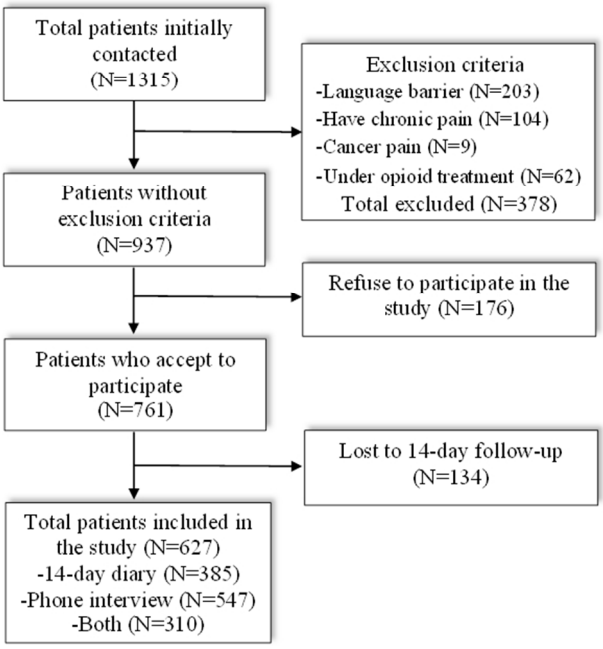

Figure 1. Flow chart of patients' enrollment in the study.

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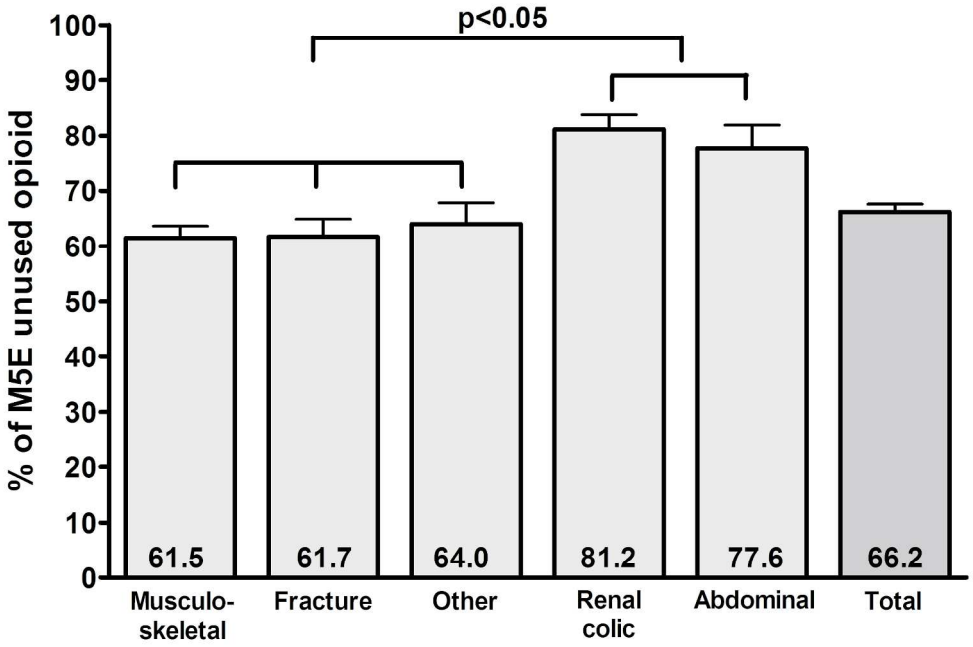

Figure 2. Percentage of morphine 5 mg equivalent pills that remained unused after the two-week follow-up for each pain condition category. Mean ± sem are reported. Brackets indicate the results of the Tukey-b multiple comparisons tests. Renal colic and abdominal pain have higher percentage of unused opioids than each of the three other pain conditions.

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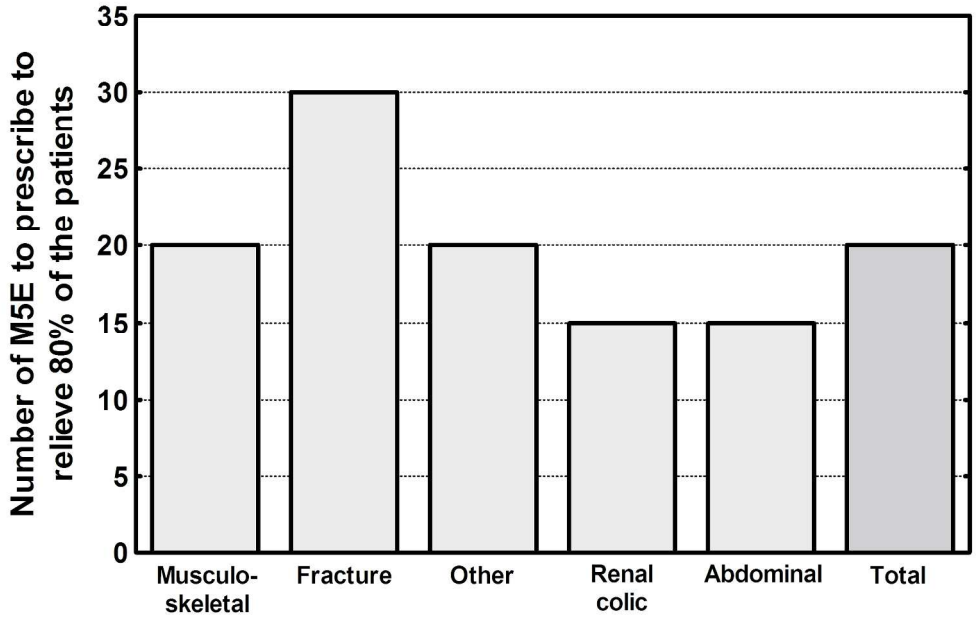

Figure 3. Number of morphine 5 mg equivalent pills to prescribe to supply 80% of patients for each pain condition category.

237x169mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses Page 6
Methods		
Study design	4	Present key elements of study design early in the paper Page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 6 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 6
Bias	9	Describe any efforts to address potential sources of bias Page 8
Study size	10	Explain how the study size was arrived at Page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding

	Page 8
	(*b*) Describe any methods used to examine subgroups and interactions Page 8
	(*c*) Explain how missing data were addressed Page 9
	(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed Page 9 *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
	(*e*) Describe any sensitivity analyses No sensitivity analysis

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 9
		(b) Give reasons for non-participation at each stage Page 9
		(c) Consider use of a flow diagram Page 9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page 9
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) Page 9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time Page 10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Page 10
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Page 12 Discuss both direction and magnitude of any potential bias Page 12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 11
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 12
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Quantity of opioids consumed following an emergency department visit for acute pain: a Canadian prospective cohort study.

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Quantity of opioids consumed following an emergency department visit for acute pain: a Canadian prospective cohort study.

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Running head: Opioid use after an ED visit for acute pain

ABSTRACT

Objectives: Prescription opioid diversion is a significant contributor to the opioid misuse epidemic. We examined the quantity of opioids consumed by emergency department (ED) discharged patients after treatment for an acute pain condition (musculoskeletal, fracture, renal colic, abdominal pain, and other), and the percentage of unused opioids available for potential misuse.

Design: Prospective cohort study.

Setting: Tertiary care trauma centre academic hospital.

Participants: A convenience sample of patients ≥18 years who visited the ED for an acute pain condition (≤ 2 weeks) and were discharged with an opioid prescription. Patients completed a 14-day paper diary of daily pain medication use. To reduce lost to follow-up, participants also responded to standardized phone interview questions about their previous 14-day pain medication use.

Outcomes: Quantity of morphine 5 mg tablets (or equivalent) prescribed, consumed, and unused during a 14-day follow-up. Quantity of opioids to adequately supply 80% of patients for 2 weeks and 95% of patients for the first 3 days was also calculated.

Results: Results for 627 patients were analyzed (mean age ±SD: 51±16 years, 48% women). Patients consumed a median of 7 tablets of morphine 5 mg (32% of the total prescribed opioids). The quantity of opioids to adequately supply 80% of patients for 2 weeks was 20 tablets of morphine 5 mg for musculoskeletal pain, 30 for fracture, 15 for renal colic or abdominal pain, and 20 for other pain conditions. The quantity to adequately supply 95% of patients for the first three days was 15 tablets of morphine 5 mg.

Conclusions: Patients discharged from the ED with an acute pain condition consumed a median of fewer than 10 tablets of morphine 5 mg (or equivalent). ED physicians should consider prescribing a smaller quantity of opioids and asking the pharmacist to dispense them in portions to minimize unused opioids.

STRENGTHS AND LIMITATIONS OF THIS STUDY

-First large study to prospectively document opioids consumption after an acute pain emergency department visit.

-Use of a 14-day daily diary to document opioid consumption.

- Opioid consumption data from a diary or phone interview could be biased by self-report

-The convenience sample from one ED centre and the small sample size for less frequent pain conditions limit the generalization of our results.

INTRODUCTION

In the 1990s, physicians, who were perceived as undertreating pain, changed their practice in order to identify and treat pain more effectively.[1] Consequently, emergency department (ED) opioid prescriptions increased significantly in the last two decades.[2 3] Meanwhile, opioid misuse (i.e., intentional use for nonmedical purposes), dependence, overdoses, and deaths have increased to epidemic proportions in both the US and Canada.[4-12]

Over 10 million US citizens have misused opioids at some point in their life[13] and 82,000 Canadians (0.3% of the total population) a non-medical use of prescription opioids in 2015.[14] It is becoming increasingly clear that the availability of unused prescription opioids contributes to misuse.[15] For example, 71% of opioid abusers received them through the diversion of prescription opioids (i.e., transfer of opioids to someone other than the initial prescription holder), and in 55% of cases, these tablets were the unused medications of friends or family members.[13 16]

Some US cities and states have formulated ED opioid prescribing guidelines[17 18] and developed prescription drug monitoring programs in hopes of preventing opioid abuse and deaths.[19] These recommendations can be summarized as follows: limit the prescription to a three-day supply (30 tablets maximum), avoid prescribing long-acting opioids, and avoid refilling lost or stolen prescriptions.[20] However, these guidelines were not based on prospectively collected data, and possibly neglected patient-centered outcomes such as quantity of opioids needed for pain relief.

Prospective surgical studies have shown wide variation in the number of opioid tablets prescribed for the same surgical procedure. Moreover, 58% to 92% of the prescribed opioids were unused,[15 21-23] and the majority (91%) were not properly stored or discarded,[21] leaving them accessible for potential misuse.[24] Studies on ED opioid prescriptions draw their data from large retrospective[25 26] administrative databases, and therefore cannot distinguish between acute and chronic pain in their

patient populations. In addition, they were unable to determine whether or not (and how many) opioids were actually consumed.

The main objective of this study was to determine the quantity of opioids consumed by ED-patients discharged with an acute pain condition. Based on our pilot study,[27] we hypothesized that the quantity of opioids that was consumed during the two weeks following an ED visit for acute pain would be fewer than 10 tablets of morphine 5 mg (or equivalent).

METHODS

Patient and public involvement

This research originated from the rinsing death toll from opioids overdose. However, patients or public were not involved in the design or conduct of the study.

Study design and setting

This prospective cohort study was conducted in the ED of a tertiary care level 1 trauma centre academic hospital with an affiliated emergency medicine residency program and an annual census of approximately 65,000 ED visits (mostly adults). Approval was obtained from the local institutional ethics review board. Patients were informed that results of the study could be published and accessible upon request.

Selection of participants

Patients aged 18 years and older and treated in the ED from June 2016 to July 2017 were identified by ED physicians 24/7 and then recruited by research nurses. We included patients with an acute pain condition present for less than two weeks and discharged from ED with an opioid prescription. A convenience sample was used because we were not able to reliably determine the number of patients missed by ED physicians. We excluded patients who did not speak French or

English, were using opioid medication prior to the ED visit, stayed in the ED > 48 hours, or were suffering from cancer or chronic pain.

Measurements

ED physicians obtained patients' consent to be contacted by the research nurses to explain the study. The research nurses subsequently obtained informed consent. Patient demographic information, pain intensity at triage, arrival mode, triage priority, and length of ED stay were extracted from our computerized medical system. ED physicians entered the final diagnosis, pain intensity at discharge, and which pain medications were prescribed. Patients also received a 14-day diary in which the patient recorded for each day the quantity, the time and the name of all the pain medication consumed. Using pre-addressed and pre-stamped envelopes, these diaries were mailed back after completion. Partly because of the low percentage of the diary returned in our pilot study, two weeks post-ED visit, all patients responded were also interviewed over the phone by a research assistant and responded to five brief questions concerning their pain medication use and current pain intensity. Patients were asked if they had filled their opioid prescription; the quantity of opioids, acetaminophen, or nonsteroidal anti-inflammatory drugs (NSAIDs) they had consumed; and whether they had received and filled any new opioid prescriptions in the last two weeks. Patients were asked to report their pain on a verbal 11-point numerical rating scale (NRS) ranging from 0 to 10, where 0 represents "no pain at all" and 10 represent "the worst imaginable pain." The two-week follow-up period was chosen because acute pain usually lasts for a short time (days or a few weeks), during which most patients stop taking opioids (88% in our pilot study).[27] Study data were collected and managed using REDCap (Research Electronic Data Capture), a secure, web-based application tool hosted in the hospital.[28]

Stratification

Because different pain diagnoses have different pain resolution patterns,[29] 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 our pilot study were musculoskeletal, fracture, renal colic, and abdominal pain.[26] Our pilot data also showed that 85% of patients receiving opioids had one of these four pain conditions.[27] For a more pragmatic approach, we included a group of patients with all other uncategorized pain conditions (e.g., abscess, burn, tooth pain). These five pain condition categories served as stratification variables for our main outcomes

Outcomes

The main outcome of this study was the quantity of opioid tablets consumed during the two-week follow-up period extracted from the paper diary or phone interview (if the diary was not returned). The quantity of opioid tablets cannot be summed as it stands, due to the different potency of different opioids. In addition, dosages vary across opioid types. In order to compare the different opioid forms, each opioid prescription and consumption was transformed into tablets of morphine 5 mg equivalent[29 30] , using Berdine and Nesbit's[31] method. A dosage of 3.33 mg of oxycodone and 1.25 mg of hydromorphone were considered equipotent to one morphine 5 mg tablet. The second outcome was the percentage of prescribed opioid tablets that were unused after the two-week follow-up. The third outcome was determined as the number of morphine 5 mg tablets (or equivalent) that would adequately supply for two weeks 80% of patients. Although not supported by any consensus, the 80% threshold was used in a recent surgical study by Hill[15] and could provide a reasonable balance between sufficient pain treatments for a large majority of patients while limiting the quantity of unused opioids. Since some US cities and states have formulated ED opioid prescribing recommendations to limit the prescription to a three-day supply (30 tablets maximum), we extracted from the 14-day diary the quantity of morphine 5 mg tablets (or equivalent) to adequately supply 95% of patients during the first three days after ED discharge. To facilitate application of the optimal prescription quantities in a clinical setting, each patient's morphine 5 mg tablets (or equivalent) consumption was grouped into

five-tablet bins (0=0; 1 to 5=5, 6 to 10=10; up to a maximum number of five tablets) before threshold calculations.

Because different pain diagnoses have different pain resolution patterns,[32] we expected the quantity of opioids required to treat acute pain to vary across pain conditions. The most frequently reported pain conditions encountered in the ED are musculoskeletal, fracture, renal colic, and abdominal pain.[26] Our pilot data from HSCM show that 85% of patients receiving opioids had one of these four pain conditions.[27] For a more pragmatic approach, we included a group of patients with all other previously undefined pain conditions (e.g., abscess, burn, tooth pain). These five pain condition categories served as stratification variables for our main outcomes.

Analysis

The study sample size was estimated based on our pilot study, where we observed a consumption of 8.8 opioid tablets (SD=10) during a two-week follow-up.[27] To detect a significant difference from the null hypothesis (H_0=10) using a Wilcoxon test assuming non-parametric distribution, we had to recruit at least 499 patients to achieve a power of at least 0.80 with an alpha of 0.05 using a one-tailed test (PASS version 11.0; NCSS, LLC. Kaysville, Utah).

The concordance between the 14-day diary and phone interview on the quantity of morphine 5 mg tablets (or equivalent) consumed was assessed with intraclass correlation coefficient. The quantity of consumed pain medication is presented as a median with inter quartile range (IRQ), since it was not normally distributed. Mann–Whitney U tests were used to assess the effect of sex and age (<65 vs ≥65) on the quantity of morphine 5 mg tablets (or equivalent) consumed. Wilcoxon signed rank tests were performed to compare the quantity of consumed morphine 5 mg tablets (or equivalent) to the null hypothesis (<10 tablets). The Kruskal–Wallis test was used to compare the quantity of consumed morphine 5 mg tablets (or equivalent) across pain conditions. Two-by-two comparisons of the quantity of consumed morphine 5 mg tablets (or equivalent) across pain conditions were made using Mann–

Whitney U tests with Bonferroni correction for multiple testing. Finally, one-way anova with Tukey-b post-hoc comparison tests were used to compare the percentage of unused opioids across pain conditions. Alpha level was set at 0.05, and all statistics were performed using SPSS version 23 (IBM, Somers, NY).

RESULTS

Description of study cohort

During our one-year recruitment period, a total of 1315 patients meeting the inclusion criteria were initially contacted. Of these, 29% had exclusion criteria (64% for language barrier, 33% for having chronic pain, and 3% for cancer pain), 13% declined to participate, and 10% could not be reached for the 14-day follow-up, leaving 627 participants (Figure 1). Non-participating and included patients were similar on all baseline characteristics (Table 1). Patients' mean age was 51 (±16) years, 48% were female, and mean pain intensity at triage was 7.8, decreasing to 4.8 at ED discharge. Among the 627 participants, 385 (61%) of them returned the 14-day diary, 547 (87%) patients responded to the phone interview, and 310 (49%) had completed both assessments. Intraclass correlation coefficient performed on opioids consumed was 0.72 (95%CI: 0.66-0.77) between the 14-day diary and phone interview which is considered good concordance between both measures.[33] Furthermore, the median number of morphine 5 mg tablets consumed was the same (6.7) for both phone interview and the 14-day diary. Therefore, data from the phone interview was used for patients with missing the 14-day diary.

Opioid consumption

Almost all patients filled their opioid prescription during the two-week follow-up period (95%). The median quantity of prescribed morphine 5 mg tablets was 30 (IQR: 28), and similar across all pain condition categories, varying from 24 to 34 tablets of morphine 5 mg (Table 2). Variability in the

consumed pain medication for the "other" pain condition category was similar to that of the four more common pain condition categories, suggesting that this patient group is comparable. The median quantity of consumed morphine 5 mg tablets was low (7, IQR: 15) compared to the prescribed quantity, and differed significantly from the null hypothesis (H0:<10; p<0.001). The consumed quantity varied significantly across pain condition categories: from 3 tablets of morphine 5 mg for renal colic to 11 tablets morphine 5 mg for fracture (p<0.001). Multiple comparisons showed that patients suffering from renal colic and abdominal pain consumed fewer opioids than those suffering from musculoskeletal pain or fracture (all p<0.05). There was no significant effect of age (<65 vs ≥65) or sex on the quantity of consumed opioids during the two-week follow-up (p>0.40 for both). Of the whole sample, 79% consumed opioids, 68% used acetaminophen, and 45% used NSAIDs.

Percentage of unused opioids

Over the course of this study, patients discharged from the ED were prescribed 23,402 tablets of morphine 5 mg, of which 7,353 were consumed during the two-week follow-up period, leaving a total of 16,049 (68%) unused morphine 5 mg tablets. The percentage of unused opioids showed significant differences across pain conditions (p<0.01): patients suffering from renal colic and abdominal pain conditions did not use 81% and 78% of their opioids, respectively, and these were significantly higher than patients suffering from musculoskeletal, fracture, or "other" pain condition (62% when averaging 3 categories; Figure 2).

Quantity of opioids to prescribe

Patients' pain intensity at two weeks was low (2.0 average) across all pain conditions. Only a minority of patients (<7%) filled a supplemental opioid prescription, indicating that the initial prescriptions were sufficient to treat pain for 93% of patients during the two-week period. The quantity of morphine 5 mg tablets to prescribe in order to adequately supply 80% the patients for two weeks was 20 for musculoskeletal pain, 30 for fracture, 15 for renal colic or abdominal pain, and 20 for other

pain conditions . Patients suffering from renal colic or abdominal pain required only half the quantity compared to patients suffering from fractures (Figure 3). The quantity of morphine 5 mg tablets to adequately supply 95% of patients during the first three days after ED discharge was 15.

DISCUSSION

This prospective study showed that patients discharged from the ED with an acute pain condition consumed a median of only 7 tablets of morphine 5 mg (or equivalent) but received a median of 30 tablets of morphine 5 mg (or equivalent) prescription, leaving two thirds of the opioids unused and available for misuse. Furthermore, patients with renal colic or abdominal pain tended to consume fewer opioids during the two-week follow-up compared to patients with musculoskeletal pain or fractures. We also determined that 20 tablets of morphine 5 mg (or equivalent) could adequately supply 80% of patients while limiting the quantity of unused opioids.

The number of opioids prescribed to patients discharged from the ED with a pain condition in this study was similar to that reported for patients who had upper extremity surgery,[22] common general surgical procedures,[15] and urological surgery.[21] This one-size-fits-all approach, which does not take into account the patient's individual condition, can probably be attributed to the lack of clinical data on opioid consumption.[17 18] During the two-week follow-up, our 68% of opioids left unused is also within the range of percentages observed in surgical studies (58–92%).[15 21-23]. The purpose of this over-prescribing may be to offset the inconvenience, for both patient and physician, of return visits to the ED or another medical service to obtain another prescription.[15] However, these large quantities of unused opioids can be diverted to family and friends, resulting in misuse, dependence, and possibly death by overdose.[21]

Patients suffering from renal colic and abdominal pain needed fewer opioids than those suffering from a fracture or musculoskeletal pain. Rodgers et al. also reported differences in opioid

consumption between different types of surgery, finding that bone surgery required more opioids than soft tissue procedures.[22] Furthermore, renal colic shows a unique pain resolution pattern: episodic intense pain until the stone is expelled. These results underscore the need for practitioners to adjust their opioid prescriptions to the type of pain condition. If patients in our study were prescribed opioids in order to adequately supply 80% of the patients (20 tablets of morphine 5 mg or equivalent), a total of 10,492 (45%) tablets would not have been available for potential misuse. Since 7 tablets of morphine 5 mg (median consumed) would adequately supply 50% of patients, another way of limiting the quantity of unused opioids would require the pharmacist to divide the opioid prescription into portions. Even if repeatable opioid prescriptions are not allowed in most settings, physicians can prescribe a fixed quantity of opioids while instructing the pharmacist to only supply a fraction at a time. For example, a physician could prescribe 15 tablets of morphine 5 mg for a renal colic (and be sure to supply adequately 80% of patients for 2 weeks) and ask the pharmacist to supply only 5 tablets at a time with an expiration date of the prescription in two weeks. For physicians with an ED opioid prescribing recommendations to limit the prescription to a three-day supply (30 tablets maximum), 15 tablets of morphine 5 mg (or equivalent) would adequately supply 95% of patients for that period and limit unused opioids. Opioids consumption could also be reduced if physicians instructed patients to use acetaminophen and/or NSAIDs first to reduce their pain before using opioids.

This trial has certain limitations. The convenience sample (investigators could not reliably determine the number of missed patients) from one ED centre and the small sample size for less frequent pain conditions (especially abdominal pain) limit the generalization of our results. However, patients were recruited 24/7, and consecutive recruitment was limited only by the fact that the investigators could not reliably determine the number of patients missed by ED physicians. It is also possible that other hospitals with different populations or different approach to pain management (ex: adequate dose of non-opioid analgesic first) could change opioid consumption.. Moreover, the reasons

for the participants to stop consuming opioids were not recorded. Some patients may have restricted their opioid use due to adverse effects, fear of addiction, or fear of running out of tablets, among others. There is a need for a multi-centre prospective study with larger sample sizes for each pain condition, to determine the impacts on the quantity of unused opioids and incidences of misuse, dependence, and opioid overdose.

In summary, patients who are discharged from the ED with an acute pain condition consumed a median of fewer than 10 tablets of morphine 5 mg (or equivalent) during the following two weeks, accounting for only one third of the prescribed opioids, leaving two thirds of the opioids unused and available for potential misuse. The quantity of opioids to adequately supply 80% of patients for two weeks was 20 tablets of morphine 5 mg (or equivalent) for musculoskeletal pain, 30 for fracture, 15 for renal colic or abdominal pain, and 20 for other pain conditions. Also, 15 tablets of morphine 5 mg (or equivalent) would adequately supply 95% of patients for the first three days. ED physicians should consider prescribing a smaller quantity of opioids and asking the pharmacist to dispense them in portions to minimize unused opioids. These results should be confirmed in a multi-centre prospective study

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Figure legends

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

Figure 2. Percentage of morphine 5 mg equivalent tablets that remained unused after the two-week follow-up for each pain condition category. Mean ± sem are reported. Brackets indicate the results of the Tukey-b multiple comparisons tests. Renal colic and abdominal pain have higher percentage of unused opioids than each of the three other pain conditions.

Figure 3. Number of morphine 5 mg tablets (or equivalent) to prescribe to supply 80% of patients for each pain condition category.

Table 1. Comparison of baseline characteristics between included and excluded (refused to participate or were lost to the 14-day follow-up) patients.

Baseline characteristics	Included (N=627)	Excluded (N=310)
Mean age (±SD)	51.0 (15.9)	50.0 (17.8)
Female (%)	47.8	49.0
ED arrival mode (%)		
-By himself	78.6	79.9
-By ambulance	21.3	20.1
High (level 1 or 2) triage priority (%)	42.6	45.3
Mean pain intensity (0-10 scale) at triage (±SD)	7.8 (2.0)	8.0 (1.7)
ED treatment section (%)		
-Ambulatory	64.6	64.1
-On stretcher	35.4	35.9
Type of pain conditions (%)		
-Musculoskeletal pain	44.0	40.3
-Fracture	19.1	19.7
-Renal colic	17.0	17.7
-Abdominal pain	6.0	5.2
-Other	13.9	17.1
Received a Tylenol prescription at ED discharged (%)	71.6	70.3
Received a NSAIDs prescription at ED discharged (%)	45.8	47.4
Opioid prescription type (%)		
-Morphine	43.6	42.7
-Oxycodone	40.5	36.9
-Hydromorphone	15.9	20.4
Median (IQR) morphine 5 mg equivalent tablets prescription	30 (28)	30 (25)
Median (IQR) ED stay (hours)	5.3 (3.6-7.7)	5.2 (3.7-7.9)
Mean (±SD) pain intensity (0-10 scale) at ED discharge	4.8 (2.9)	4.7 (2.9)

IQR: inter-quartile range; NSAIDs: nonsteroidal anti-inflammatory drug

Table 2. Pain intensity and pain medication for each pain condition during the two-week follow-up.

Variables	Musculo-squeletal	Fracture	Renal colic	Abdominal	Other	Total
Number of patients	280	119	106	37	85	627
Mean (±SD) pain intensity at ED discharged	5.6 (2.4)	5.2 (2.6)	1.9 (2.7)	3.7 (3.2)	5.5 (3.0)	4.8 (2.9)
Mean (±SD) pain intensity at two-week	2.6 (2.7)	2.6 (2.9)	0.5 (1.2)	1.6 (2.8)	1.8 (2.6)	2.0 (2.6)
Filled opioid prescription (%)	95.1	90.4	99.0	97.1	91.4	94.5
Patients who filled another opioid prescription (n, %)	22 (7.9)	10 (8.4)	3 (2.8)	2 (5.4)	5 (5.9)	42 (6.7)
Median (IQR) number of morphine 5 mg prescribed	30 (28)	34 (30)	31 (25)	30 (19)	24 (26)	30 (28)
Median (IQR) number of morphine 5 mg consumed	8 (17)	11 (20)	3 (10)	3 (8)	6 (14)	7 (15)
Received acetaminophen prescription at discharged (%)	78.2	79.0	57.5	56.8	63.5	71.6
Consumed acetaminophen (%)	73.9	87.4	49.1	48.6	52.9	67.9
Received NSAIDs prescription at discharged (%)	49.3	28.6	64.2	40.5	37.6	45.8
Consumed NSAIDs (%)	51.8	35.3	50.9	35.1	34.1	45.1

IQR: inter-quartile range; tablet; NSAIDs: nonsteroidal anti-inflammatory drugs

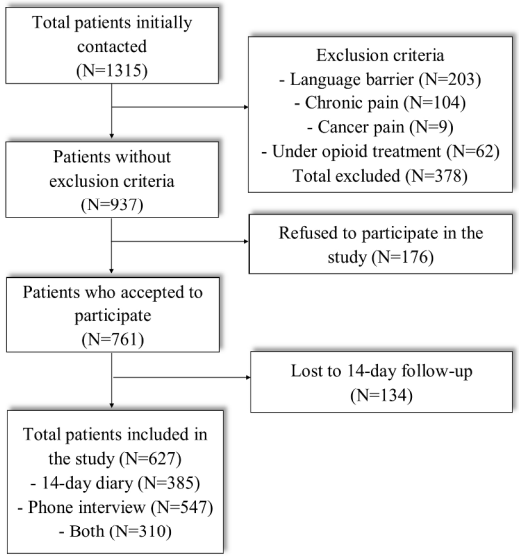

Figure 1. Flow chart of patients' enrollment in the study.

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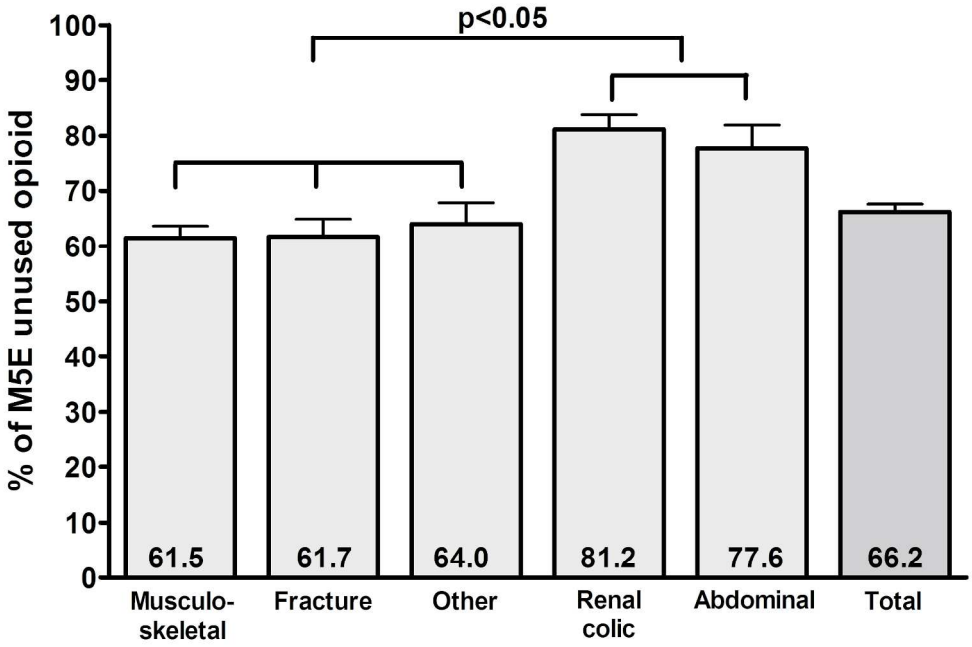

Figure 2. Percentage of morphine 5 mg equivalent pills that remained unused after the two-week follow-up for each pain condition category. Mean ± sem are reported. Brackets indicate the results of the Tukey-b multiple comparisons tests. Renal colic and abdominal pain have higher percentage of unused opioids than each of the three other pain conditions.

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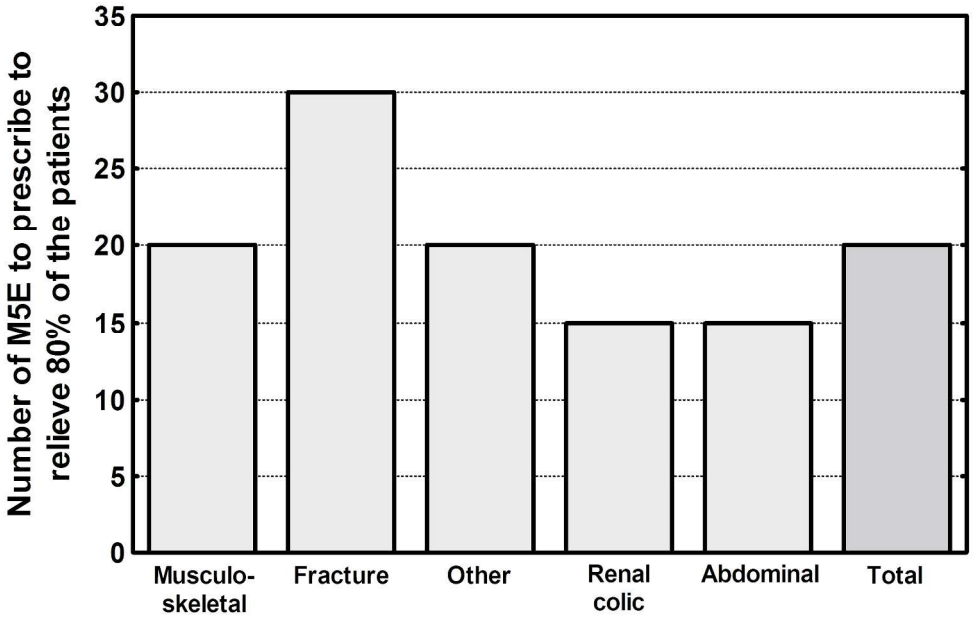

Figure 3. Number of morphine 5 mg equivalent pills to prescribe to supply 80% of patients for each pain condition category.

237x169mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses Page 6
Methods		
Study design	4	Present key elements of study design early in the paper Page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 6 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 6
Bias	9	Describe any efforts to address potential sources of bias Page 8
Study size	10	Explain how the study size was arrived at Page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding

	Page 8
	(*b*) Describe any methods used to examine subgroups and interactions Page 8
	(*c*) Explain how missing data were addressed Page 9
	(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed Page 9 *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
	(*e*) Describe any sensitivity analyses No sensitivity analysis

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 9
		(b) Give reasons for non-participation at each stage Page 9
		(c) Consider use of a flow diagram Page 9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page 9
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) Page 9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time Page 10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Page 10
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Page 12 Discuss both direction and magnitude of any potential bias Page 12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 11
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 12
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Quantity of opioids consumed following an emergency department visit for acute pain: a Canadian prospective cohort study.

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Quantity of opioids consumed following an emergency department visit for acute pain: a Canadian prospective cohort study.

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R.D. and J.M.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 analysis. R.D. drafted the manuscript, and A. C.., E.P., J.M., S.G., M.E., G.L., J.L. 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.

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Running head: Opioid use after an ED visit for acute pain

ABSTRACT

Objectives: Prescription opioid diversion is a significant contributor to the opioid misuse epidemic. We examined the quantity of opioids consumed by emergency department (ED) discharged patients after treatment for an acute pain condition (musculoskeletal, fracture, renal colic, abdominal pain, and other), and the percentage of unused opioids available for potential misuse.

Design: Prospective cohort study.

Setting: Tertiary care trauma centre academic hospital.

Participants: A convenience sample of patients ≥18 years who visited the ED for an acute pain condition (≤ 2 weeks) and were discharged with an opioid prescription. Patients completed a 14-day paper diary of daily pain medication use. To reduce lost to follow-up, participants also responded to standardized phone interview questions about their previous 14-day pain medication use.

Outcomes: Quantity of morphine 5 mg tablets (or equivalent) prescribed, consumed, and unused during a 14-day follow-up. Quantity of opioids to adequately supply 80% of patients for 2 weeks and 95% of patients for the first 3 days was also calculated.

Results: Results for 627 patients were analyzed (mean age ±SD: 51±16 years, 48% women). Patients consumed a median of 7 tablets of morphine 5 mg (32% of the total prescribed opioids). The quantity of opioids to adequately supply 80% of patients for 2 weeks was 20 tablets of morphine 5 mg for musculoskeletal pain, 30 for fracture, 15 for renal colic or abdominal pain, and 20 for other pain conditions. The quantity to adequately supply 95% of patients for the first three days was 15 tablets of morphine 5 mg.

Conclusions: Patients discharged from the ED with an acute pain condition consumed a median of fewer than 10 tablets of morphine 5 mg (or equivalent). ED physicians should consider prescribing a smaller quantity of opioids and asking the pharmacist to dispense them in portions to minimize unused opioids.

STRENGTHS AND LIMITATIONS OF THIS STUDY

-First large study to prospectively document opioids consumption after an acute pain emergency department visit.

-Use of a 14-day daily diary to document opioid consumption.

- Opioid consumption data from a diary or phone interview could be biased by self-report

-The convenience sample from one ED centre and the small sample size for less frequent pain conditions limit the generalization of our results.

INTRODUCTION

In the 1990s, physicians, who were perceived as undertreating pain, changed their practice in order to identify and treat pain more effectively.[1] Consequently, emergency department (ED) opioid prescriptions increased significantly in the last two decades.[2 3] Meanwhile, opioid misuse (i.e., intentional use for nonmedical purposes), dependence, overdoses, and deaths have increased to epidemic proportions in both the US and Canada.[4-12]

Over 10 million US citizens have misused opioids at some point in their life[13] and 82,000 Canadians (0.3% of the total population) a non-medical use of prescription opioids in 2015.[14] It is becoming increasingly clear that the availability of unused prescription opioids contributes to misuse.[15] For example, 71% of opioid abusers received them through the diversion of prescription opioids (i.e., transfer of opioids to someone other than the initial prescription holder), and in 55% of cases, these tablets were the unused medications of friends or family members.[13 16]

Some US cities and states have formulated ED opioid prescribing guidelines[17 18] and developed prescription drug monitoring programs in hopes of preventing opioid abuse and deaths.[19] These recommendations can be summarized as follows: limit the prescription to a three-day supply (30 tablets maximum), avoid prescribing long-acting opioids, and avoid refilling lost or stolen prescriptions.[20] However, these guidelines were not based on prospectively collected data, and possibly neglected patient-centered outcomes such as quantity of opioids needed for pain relief.

Prospective surgical studies have shown wide variation in the number of opioid tablets prescribed for the same surgical procedure. Moreover, 58% to 92% of the prescribed opioids were unused,[15 21-23] and the majority (91%) were not properly stored or discarded,[21] leaving them accessible for potential misuse.[24] A study on ED opioid prescriptions draw their data from large retrospective[25] administrative databases, and did not distinguish between acute and chronic pain in their patient

populations. In addition, they were unable to determine whether or not (and how many) opioids were actually consumed.

The main objective of this study was to determine the quantity of opioids consumed by ED-patients discharged with an acute pain condition. Based on our pilot study,[26] we hypothesized that the quantity of opioids that was consumed during the two weeks following an ED visit for acute pain would be fewer than 10 tablets of morphine 5 mg (or equivalent).

METHODS

Patient and public involvement

This research originated from the rinsing death toll from opioids overdose. However, patients or public were not involved in the design or conduct of the study.

Study design and setting

This prospective cohort study was conducted in the ED of a tertiary care level 1 trauma centre academic hospital with an affiliated emergency medicine residency program and an annual census of approximately 65,000 ED visits (mostly adults). Approval was obtained from the local institutional ethics review board. Patients were informed that results of the study could be published and accessible upon request.

Selection of participants

Patients aged 18 years and older and treated in the ED from June 2016 to July 2017 were identified by ED physicians 24/7 and then recruited by research nurses. We included patients with an acute pain condition present for less than two weeks and discharged from ED with an opioid prescription. A convenience sample was used because we were not able to reliably determine the number of patients missed by ED physicians. We excluded patients who did not speak French or

English, were using opioid medication prior to the ED visit, stayed in the ED > 48 hours, or were suffering from cancer or chronic pain.

Measurements

ED physicians obtained patients' consent to be contacted by the research nurses to explain the study. The research nurses subsequently obtained informed consent. Patient demographic information, pain intensity at triage, arrival mode, triage priority, and length of ED stay were extracted from our computerized medical system. ED physicians entered the final diagnosis, pain intensity at discharge, and which pain medications were prescribed. Patients also received a 14-day diary in which the patient recorded for each day the quantity, the time and the name of all the pain medication consumed. Using pre-addressed and pre-stamped envelopes, these diaries were mailed back after completion. Partly because of the low percentage of the diary returned in our pilot study, two weeks post-ED visit, all patients responded were also interviewed over the phone by a research assistant and responded to five brief questions concerning their pain medication use and current pain intensity. Patients were asked if they had filled their opioid prescription; the quantity of opioids, acetaminophen, or nonsteroidal anti-inflammatory drugs (NSAIDs) they had consumed; and whether they had received and filled any new opioid prescriptions in the last two weeks. Patients were asked to report their pain on a verbal 11-point numerical rating scale (NRS) ranging from 0 to 10, where 0 represents "no pain at all" and 10 represent "the worst imaginable pain." The two-week follow-up period was chosen because acute pain usually lasts for a short time (days or a few weeks), during which most patients stop taking opioids (88% in our pilot study).[26] Study data were collected and managed using REDCap (Research Electronic Data Capture), a secure, web-based application tool hosted in the hospital.[27]

Stratification

Because different pain diagnoses have different pain resolution patterns,[28] 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 our pilot study were musculoskeletal, fracture, renal colic, and abdominal pain.[25] Our pilot data also showed that 85% of patients receiving opioids had one of these four pain conditions.[26] For a more pragmatic approach, we included a group of patients with all other uncategorized pain conditions (e.g., abscess, burn, tooth pain). These five pain condition categories served as stratification variables for our main outcomes

Outcomes

The main outcome of this study was the quantity of opioid tablets consumed during the two-week follow-up period extracted from the paper diary or phone interview (if the diary was not returned). The quantity of opioid tablets cannot be summed as it stands, due to the different potency of different opioids. In addition, dosages vary across opioid types. In order to compare the different opioid forms, each opioid prescription and consumption was transformed into tablets of morphine 5 mg equivalent[29 30] , using Berdine and Nesbit's[31] method. A dosage of 3.33 mg of oxycodone and 1.25 mg of hydromorphone were considered equipotent to one morphine 5 mg tablet. The second outcome was the percentage of prescribed opioid tablets that were unused after the two-week follow-up. The third outcome was determined as the number of morphine 5 mg tablets (or equivalent) that would adequately supply for two weeks 80% of patients. Although not supported by any consensus, the 80% threshold was used in a recent surgical study by Hill[15] and could provide a reasonable balance between sufficient pain treatments for a large majority of patients while limiting the quantity of unused opioids. Since some US cities and states have formulated ED opioid prescribing recommendations to limit the prescription to a three-day supply (30 tablets maximum), we extracted from the 14-day diary the quantity of morphine 5 mg tablets (or equivalent) to adequately supply 95% of patients during the first three days after ED discharge. To facilitate application of the optimal prescription quantities in a clinical setting, each patient's morphine 5 mg tablets (or equivalent) consumption was grouped into

five-tablet bins (0=0; 1 to 5=5, 6 to 10=10; up to a maximum number of five tablets) before threshold calculations.

Because different pain diagnoses have different pain resolution patterns,[28] we expected the quantity of opioids required to treat acute pain to vary across pain conditions. The most frequently reported pain conditions encountered in the ED are musculoskeletal, fracture, renal colic, and abdominal pain.[25] Our pilot data from HSCM show that 85% of patients receiving opioids had one of these four pain conditions.[26] For a more pragmatic approach, we included a group of patients with all other previously undefined pain conditions (e.g., abscess, burn, tooth pain). These five pain condition categories served as stratification variables for our main outcomes.

Analysis

The study sample size was estimated based on our pilot study, where we observed a consumption of 8.8 opioid tablets (SD=10) during a two-week follow-up.[26] To detect a significant difference from the null hypothesis (H_0=10) using a Wilcoxon test assuming non-parametric distribution, we had to recruit at least 499 patients to achieve a power of at least 0.80 with an alpha of 0.05 using a one-tailed test (PASS version 11.0; NCSS, LLC. Kaysville, Utah).

The concordance between the 14-day diary and phone interview on the quantity of morphine 5 mg tablets (or equivalent) consumed was assessed with intraclass correlation coefficient. The quantity of consumed pain medication is presented as a median with inter quartile range (IRQ), since it was not normally distributed. Mann–Whitney U tests were used to assess the effect of sex and age (<65 vs ≥65) on the quantity of morphine 5 mg tablets (or equivalent) consumed. Wilcoxon signed rank tests were performed to compare the quantity of consumed morphine 5 mg tablets (or equivalent) to the null hypothesis (<10 tablets). The Kruskal–Wallis test was used to compare the quantity of consumed morphine 5 mg tablets (or equivalent) across pain conditions. Two-by-two comparisons of the quantity of consumed morphine 5 mg tablets (or equivalent) across pain conditions were made using Mann–

Whitney U tests with Bonferroni correction for multiple testing. Finally, one-way anova with Tukey-b post-hoc comparison tests were used to compare the percentage of unused opioids across pain conditions. Alpha level was set at 0.05, and all statistics were performed using SPSS version 23 (IBM, Somers, NY).

RESULTS

Description of study cohort

During our one-year recruitment period, a total of 1315 patients meeting the inclusion criteria were initially contacted. Of these, 29% had exclusion criteria (64% for language barrier, 33% for having chronic pain, and 3% for cancer pain), 13% declined to participate, and 10% could not be reached for the 14-day follow-up, leaving 627 participants (Figure 1). Non-participating and included patients were similar on all baseline characteristics (Table 1). Patients' mean age was 51 (±16) years, 48% were female, and mean pain intensity at triage was 7.8, decreasing to 4.8 at ED discharge. Among the 627 participants, 385 (61%) of them returned the 14-day diary, 547 (87%) patients responded to the phone interview, and 310 (49%) had completed both assessments. Intraclass correlation coefficient performed on opioids consumed was 0.72 (95%CI: 0.66-0.77) between the 14-day diary and phone interview which is considered good concordance between both measures.[32] Furthermore, the median number of morphine 5 mg tablets consumed was the same (6.7) for both phone interview and the 14-day diary. Therefore, data from the phone interview was used for patients with missing the 14-day diary.

Opioid consumption

Almost all patients filled their opioid prescription during the two-week follow-up period (95%). The median quantity of prescribed morphine 5 mg tablets was 30 (IQR: 28), and similar across all pain condition categories, varying from 24 to 34 tablets of morphine 5 mg (Table 2). Variability in the

consumed pain medication for the "other" pain condition category was similar to that of the four more common pain condition categories, suggesting that this patient group is comparable. The median quantity of consumed morphine 5 mg tablets was low (7, IQR: 15) compared to the prescribed quantity, and differed significantly from the null hypothesis (H0:<10; p<0.001). The consumed quantity varied significantly across pain condition categories: from 3 tablets of morphine 5 mg for renal colic to 11 tablets morphine 5 mg for fracture (p<0.001). Multiple comparisons showed that patients suffering from renal colic and abdominal pain consumed fewer opioids than those suffering from musculoskeletal pain or fracture (all p<0.05). There was no significant effect of age (<65 vs ≥65) or sex on the quantity of consumed opioids during the two-week follow-up (p>0.40 for both). Of the whole sample, 79% consumed opioids, 68% used acetaminophen, and 45% used NSAIDs.

Percentage of unused opioids

Over the course of this study, patients discharged from the ED were prescribed 23,402 tablets of morphine 5 mg, of which 7,353 were consumed during the two-week follow-up period, leaving a total of 16,049 (68%) unused morphine 5 mg tablets. The percentage of unused opioids showed significant differences across pain conditions (p<0.01): patients suffering from renal colic and abdominal pain conditions did not use 81% and 78% of their opioids, respectively, and these were significantly higher than patients suffering from musculoskeletal, fracture, or "other" pain condition (62% when averaging 3 categories; Figure 2).

Quantity of opioids to prescribe

Patients' pain intensity at two weeks was low (2.0 average) across all pain conditions. Only a minority of patients (<7%) filled a supplemental opioid prescription, indicating that the initial prescriptions were sufficient to treat pain for 93% of patients during the two-week period. The quantity of morphine 5 mg tablets to prescribe in order to adequately supply 80% the patients for two weeks was 20 for musculoskeletal pain, 30 for fracture, 15 for renal colic or abdominal pain, and 20 for other

pain conditions . Patients suffering from renal colic or abdominal pain required only half the quantity compared to patients suffering from fractures (Figure 3). The quantity of morphine 5 mg tablets to adequately supply 95% of patients during the first three days after ED discharge was 15.

DISCUSSION

This prospective study showed that patients discharged from the ED with an acute pain condition consumed a median of only 7 tablets of morphine 5 mg (or equivalent) but received a median of 30 tablets of morphine 5 mg (or equivalent) prescription, leaving two thirds of the opioids unused and available for misuse. Furthermore, patients with renal colic or abdominal pain tended to consume fewer opioids during the two-week follow-up compared to patients with musculoskeletal pain or fractures. We also determined that 20 tablets of morphine 5 mg (or equivalent) could adequately supply 80% of patients while limiting the quantity of unused opioids.

The number of opioids prescribed to patients discharged from the ED with a pain condition in this study was similar to that reported for patients who had upper extremity surgery,[22] common general surgical procedures,[15] and urological surgery.[21] This one-size-fits-all approach, which does not take into account the patient's individual condition, can probably be attributed to the lack of clinical data on opioid consumption.[17 18] During the two-week follow-up, our 68% of opioids left unused is also within the range of percentages observed in surgical studies (58–92%).[15 21-23]. The purpose of this over-prescribing may be to offset the inconvenience, for both patient and physician, of return visits to the ED or another medical service to obtain another prescription.[15] However, these large quantities of unused opioids can be diverted to family and friends, resulting in misuse, dependence, and possibly death by overdose.[21]

Patients suffering from renal colic and abdominal pain needed fewer opioids than those suffering from a fracture or musculoskeletal pain. Rodgers et al. also reported differences in opioid

consumption between different types of surgery, finding that bone surgery required more opioids than soft tissue procedures.[22] Furthermore, renal colic shows a unique pain resolution pattern: episodic intense pain until the stone is expelled. These results underscore the need for practitioners to adjust their opioid prescriptions to the type of pain condition. If patients in our study were prescribed opioids in order to adequately supply 80% of the patients (20 tablets of morphine 5 mg or equivalent), a total of 10,492 (45%) tablets would not have been available for potential misuse. Since 7 tablets of morphine 5 mg (median consumed) would adequately supply 50% of patients, another way of limiting the quantity of unused opioids would require the pharmacist to divide the opioid prescription into portions. Even if repeatable opioid prescriptions are not allowed in most settings, physicians can prescribe a fixed quantity of opioids while instructing the pharmacist to only supply a fraction at a time. For example, a physician could prescribe 15 tablets of morphine 5 mg for a renal colic (and be sure to supply adequately 80% of patients for 2 weeks) and ask the pharmacist to supply only 5 tablets at a time with an expiration date of the prescription in two weeks. For physicians with an ED opioid prescribing recommendations to limit the prescription to a three-day supply (30 tablets maximum), 15 tablets of morphine 5 mg (or equivalent) would adequately supply 95% of patients for that period and limit unused opioids. Opioids consumption could also be reduced if physicians instructed patients to use acetaminophen and/or NSAIDs first to reduce their pain before using opioids.

This trial has certain limitations. The convenience sample (investigators could not reliably determine the number of missed patients) from one ED centre and the small sample size for less frequent pain conditions (especially abdominal pain) limit the generalization of our results. However, patients were recruited 24/7, and consecutive recruitment was limited only by the fact that the investigators could not reliably determine the number of patients missed by ED physicians. It is also possible that other hospitals with different populations or different approach to pain management (ex: adequate dose of non-opioid analgesic first) could change opioid consumption.. Moreover, the reasons

for the participants to stop consuming opioids were not recorded. Some patients may have restricted their opioid use due to adverse effects, fear of addiction, or fear of running out of tablets, among others. There is a need for a multi-centre prospective study with larger sample sizes for each pain condition, to determine the impacts on the quantity of unused opioids and incidences of misuse, dependence, and opioid overdose.

In summary, patients who are discharged from the ED with an acute pain condition consumed a median of fewer than 10 tablets of morphine 5 mg (or equivalent) during the following two weeks, accounting for only one third of the prescribed opioids, leaving two thirds of the opioids unused and available for potential misuse. The quantity of opioids to adequately supply 80% of patients for two weeks was 20 tablets of morphine 5 mg (or equivalent) for musculoskeletal pain, 30 for fracture, 15 for renal colic or abdominal pain, and 20 for other pain conditions. Also, 15 tablets of morphine 5 mg (or equivalent) would adequately supply 95% of patients for the first three days. ED physicians should consider prescribing a smaller quantity of opioids and asking the pharmacist to dispense them in portions to minimize unused opioids. These results should be confirmed in a multi-centre prospective study

Acknowledgments

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Figure legends

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

Figure 2. Percentage of morphine 5 mg equivalent tablets that remained unused after the two-week follow-up for each pain condition category. Mean ± sem are reported. Brackets indicate the results of the Tukey-b multiple comparisons tests. Renal colic and abdominal pain have higher percentage of unused opioids than each of the three other pain conditions.

Figure 3. Number of morphine 5 mg tablets (or equivalent) to prescribe to supply 80% of patients for each pain condition category.

Table 1. Comparison of baseline characteristics between included and excluded (refused to participate or were lost to the 14-day follow-up) patients.

Baseline characteristics	Included (N=627)	Excluded (N=310)
Mean age (±SD)	51.0 (15.9)	50.0 (17.8)
Female (%)	47.8	49.0
ED arrival mode (%)		
-By himself	78.6	79.9
-By ambulance	21.3	20.1
High (level 1 or 2) triage priority (%)	42.6	45.3
Mean pain intensity (0-10 scale) at triage (±SD)	7.8 (2.0)	8.0 (1.7)
ED treatment section (%)		
-Ambulatory	64.6	64.1
-On stretcher	35.4	35.9
Type of pain conditions (%)		
-Musculoskeletal pain	44.0	40.3
-Fracture	19.1	19.7
-Renal colic	17.0	17.7
-Abdominal pain	6.0	5.2
-Other	13.9	17.1
Received a Tylenol prescription at ED discharged (%)	71.6	70.3
Received a NSAIDs prescription at ED discharged (%)	45.8	47.4
Opioid prescription type (%)		
-Morphine	43.6	42.7
-Oxycodone	40.5	36.9
-Hydromorphone	15.9	20.4
Median (IQR) morphine 5 mg equivalent tablets prescription	30 (28)	30 (25)
Median (IQR) ED stay (hours)	5.3 (3.6-7.7)	5.2 (3.7-7.9)
Mean (±SD) pain intensity (0-10 scale) at ED discharge	4.8 (2.9)	4.7 (2.9)

IQR: inter-quartile range; NSAIDs: nonsteroidal anti-inflammatory drug

Table 2. Pain intensity and pain medication for each pain condition during the two-week follow-up.

Variables	Musculo-squeletal	Fracture	Renal colic	Abdominal	Other	Total
Number of patients	280	119	106	37	85	627
Mean (±SD) pain intensity at ED discharged	5.6 (2.4)	5.2 (2.6)	1.9 (2.7)	3.7 (3.2)	5.5 (3.0)	4.8 (2.9)
Mean (±SD) pain intensity at two-week	2.6 (2.7)	2.6 (2.9)	0.5 (1.2)	1.6 (2.8)	1.8 (2.6)	2.0 (2.6)
Filled opioid prescription (%)	95.1	90.4	99.0	97.1	91.4	94.5
Patients who filled another opioid prescription (n, %)	22 (7.9)	10 (8.4)	3 (2.8)	2 (5.4)	5 (5.9)	42 (6.7)
Median (IQR) number of morphine 5 mg prescribed	30 (28)	34 (30)	31 (25)	30 (19)	24 (26)	30 (28)
Median (IQR) number of morphine 5 mg consumed	8 (17)	11 (20)	3 (10)	3 (8)	6 (14)	7 (15)
Received acetaminophen prescription at discharged (%)	78.2	79.0	57.5	56.8	63.5	71.6
Consumed acetaminophen (%)	73.9	87.4	49.1	48.6	52.9	67.9
Received NSAIDs prescription at discharged (%)	49.3	28.6	64.2	40.5	37.6	45.8
Consumed NSAIDs (%)	51.8	35.3	50.9	35.1	34.1	45.1

IQR: inter-quartile range; tablet; NSAIDs: nonsteroidal anti-inflammatory drugs

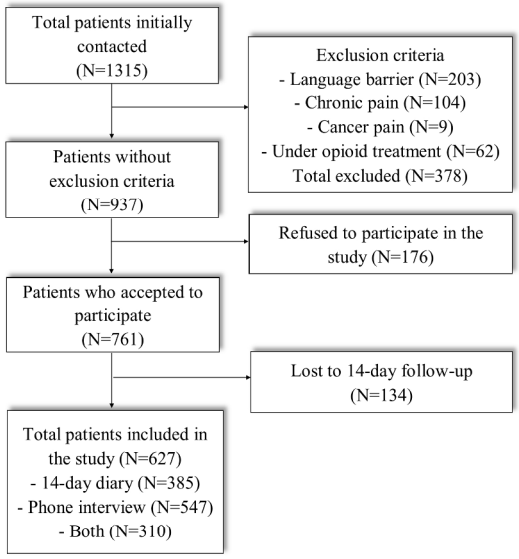

Figure 1. Flow chart of patients' enrollment in the study.

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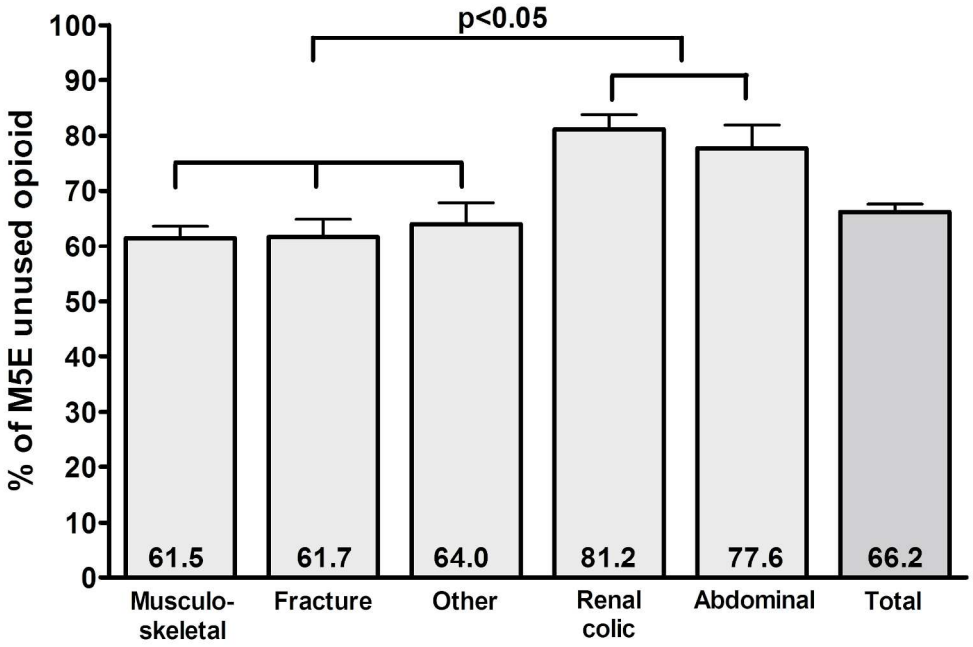

Figure 2. Percentage of morphine 5 mg equivalent pills that remained unused after the two-week follow-up for each pain condition category. Mean ± sem are reported. Brackets indicate the results of the Tukey-b multiple comparisons tests. Renal colic and abdominal pain have higher percentage of unused opioids than each of the three other pain conditions.

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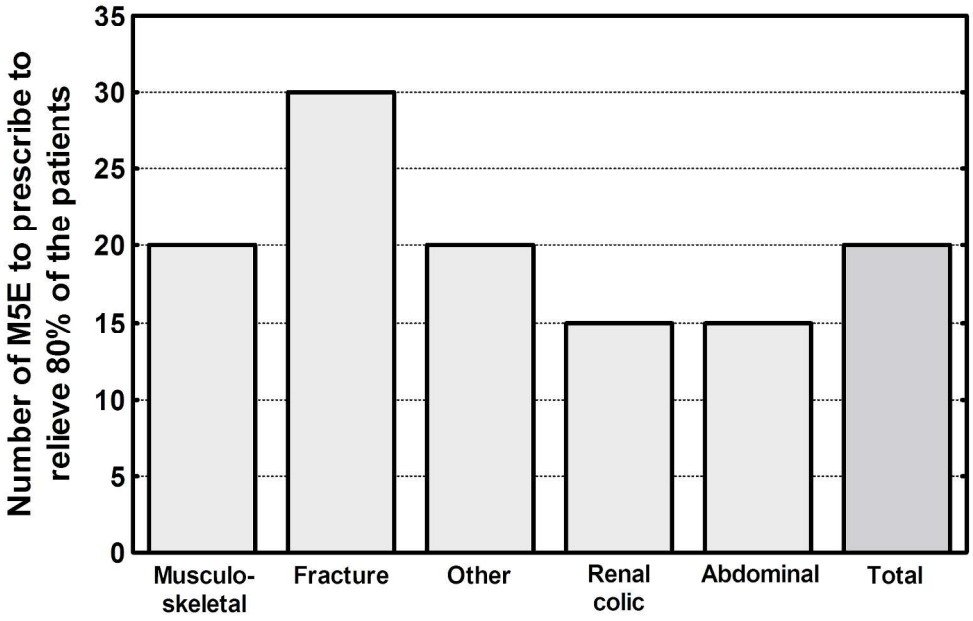

Figure 3. Number of morphine 5 mg equivalent pills to prescribe to supply 80% of patients for each pain condition category.

237x169mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Page 3
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Page 5
Objectives	3	State specific objectives, including any prespecified hypotheses Page 6
Methods		
Study design	4	Present key elements of study design early in the paper Page 6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Page 6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Page 6 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Page 7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Page 6
Bias	9	Describe any efforts to address potential sources of bias Page 8
Study size	10	Explain how the study size was arrived at Page 8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Page 8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding

	Page 8
	(*b*) Describe any methods used to examine subgroups and interactions Page 8
	(*c*) Explain how missing data were addressed Page 9
	(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed Page 9 *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
	(*e*) Describe any sensitivity analyses No sensitivity analysis

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Page 9
		(b) Give reasons for non-participation at each stage Page 9
		(c) Consider use of a flow diagram Page 9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Page 9
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount) Page 9
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time Page 10
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included Page 10
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives Page 10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Page 12 Discuss both direction and magnitude of any potential bias Page 12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Page 11
Generalisability	21	Discuss the generalisability (external validity) of the study results Page 12
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Page 1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.