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EHR-Based Medication Complete Communication Strategy to Promote Safe Opioid Use

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1. **Structured Abstract**

Purpose: The study objective was to evaluate the effect of an Electronic Medication Complete Communication (EMC^2) Opioid Strategy on patients' safe use of and knowledge about opioids.
Scope: Through a randomized controlled trial, as well as additional subanalyses, we evaluated the effect of an EHR-integrated intervention on use of and knowledge about opioids as well as explored limitations to implementation.
Methods: We conducted a three-arm prospective, randomized, controlled pragmatic trial with physician-level randomization. Discharged patients at an urban academic ED (>88,000 visits) with new hydrocodone-acetaminophen prescriptions received one of three pathways: (1) usual care (UC), (2) EMC^2 intervention, or (3) EMC^2+SMS text messaging. The ED EMC^2 intervention triggered two patient-facing tools (MedSheet, literacy-appropriate prescription wording [Take-Wait-Stop]) and three provider-facing reminders to counsel (directed to ED physician, pharmacist, follow-up physician). Patients in the EMC^2+SMS arm additionally received one text message/day for 1 week. Follow-up at 1-2 weeks assessed "demonstrated safe use" (primary outcome). Secondary outcomes of patient knowledge, implementation, cost, and acceptability were also assessed. Additional exploratory analyses were also conducted.
Results: Demonstrated safe use occurred more often in the EMC^2 group (adjusted odds ratio [aOR], 2.46; 95% CI, 1.19, 5.06) compared with UC but did not translate to actual use. Medication knowledge (composite knowledge score) was greater in the EMC^2+SMS group (beta, 0.57; 95% CI, 0.09, 1.06) than UC. The intervention was well accepted and low cost but faced barriers to implementation at the community pharmacy level.

Key Words: opioid analgesics; health literacy; text messaging; emergency

2. **Purpose**

The overall goal of our grant was to leverage an electronic health record (EHR) to implement a multifaceted strategy to better educate emergency department patients about medication risks and safe use for opioid pain relievers.

The purpose of this study was was to evaluate the effect of an Electronic Medication Complete Communication (EMC^2) Opioid Strategy on patients' safe use of opioids and knowledge about opioids after an emergency department visit for patients newly prescribed hydrocodone-acetaminophen. We secondarily sought to evaluate the fidelity of implementation of the EHR-embedded strategy and the cost and to discern barriers to intervention success and dissemination.

3. **Scope**

3.A. Background: The United States continues to face an epidemic of opioid addiction and overdose, the scale of which is unprecedented and has prompted the declaration of a public health emergency. Many interventions and guidelines appropriately target decreasing the number of opioid prescriptions and the number of pills per prescription. Yet, there has been less focus on the interaction at the time of an initial prescription to an opioid-naive patient.

3.B. Context: In settings such as the emergency department (ED), where acute or chronic pain account for almost two thirds of ED visits, use of opioids may be appropriate at times, if prescribed safely. However, little is known about how counseling in the ED influences knowledge about the medications or safe use.

3.C. Setting: This studies took place at Northwestern Memorial Hospital, an urban academic medical center in Chicago, IL, with an annual ED visit volume >88,000. Northwestern serves a diverse population with approximately half of patients from racial and ethnic minorities and one third with low income.

3.D. Participants: All attending and resident physicians and APPs based in the ED were approached for study inclusion, as their consent was needed to make changes to their individual EHR interface. After consent, physician participants were informed of the changes that would be made to their EHR and were randomized to one of three study arms.

Study participants were patients being discharged with a new prescription for hydrocodone-acetaminophen between July 2015 and August 2017. Patients were eligible for enrollment if they met the following five conditions: 1) 18 years of age or older, 2) English speaking, 3) prescribed a tablet form of hydrocodone-acetaminophen (non-liquid formulation), 4) responsible for self-administering their own medication, and 5) discharged by a provider who consented to the study. Patients were excluded if they were clinically unstable; psychologically impaired or intoxicated as judged by the research staff or ED provider; chronically taking opioids (as defined by self-report of "daily or near daily" use of opioids for the past 90 days); being admitted to the hospital; unable to complete study follow-up; or pregnant.

3.E. Incidence: At the time the study was submitted for funding in 2014, ~16% of ED discharges from the site received a new prescription for an opioid. Due to the ongoing opioid crisis and national efforts to minimize new opioid prescriptions and opioid refills from multiple providers, the rate of opioid prescribing at our site decreased significantly over the study period. By the end of the study recruitment in August 2017, ~7-8% of ED discharged from the study site receive an opioid.

4. **Methods**

4.A. Study Design: We conducted a three-arm, physician-randomized, pragmatic trial of the ED EMC^2 Opioid Strategy to improve safe use and patient knowledge of newly prescribed opioids. In brief, the primary goal of the study was to determine if the EMC^2 intervention could improve demonstrated safe use of newly prescribed opioids. As a 'point of care' intervention, the need for 'post-visit' reinforcement of the safe use educational messages was also considered. Thus, our approach was tested with and without an SMS text messaging

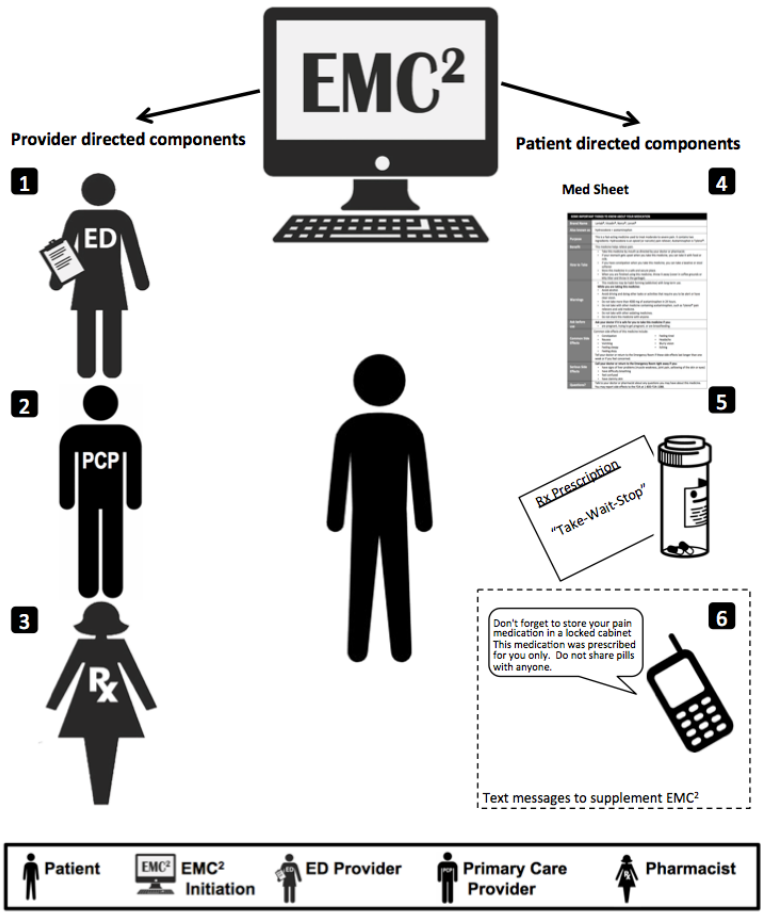
promotional component, understanding the need for a scalable follow-up component within a clinical context that does not routinely track patients beyond acute visits. Secondarily, we sought to determine if the EMC^2 intervention could increase patient knowledge about opioid pain relievers and decrease risky behaviors related to opioid use. We hypothesized that, compared with patients in the usual care arm, patients receiving EMC^2 interventions would demonstrate higher rates of safe use of their prescribed opioid as measured by a demonstrated dosing task and secondarily demonstrate higher rates of opioid-related medication knowledge.

The study had three arms, usual care and two intervention arms named EMC^2 and EMC^2+SMS Text Messaging. In the usual care (control) arm, providers had no modifications to their EHR interface, and their patients received discharge instructions, prescription instructions, and counseling about safe use per that provider's customary practice. For providers randomly assigned to the EMC^2 arm, the three provider-facing functions were 'turned on,' and their patients were eligible to receive two of the educational materials from the ED EMC^2 Opioid Strategy. Patients of providers in the EMC^2+SMS text-messaging arm also received daily text messages to prompt safe use for 1 week following their ED visit.

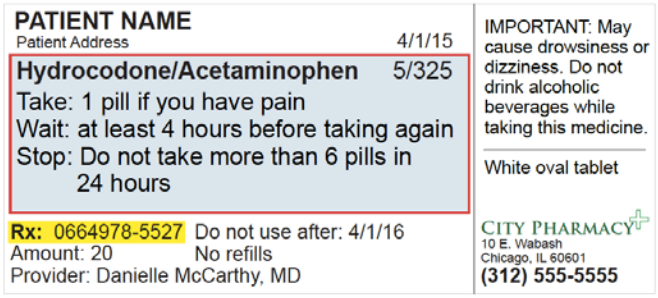
4.B. Data Sources: Data were derived from six sources: 1) the electronic health record, 2) patient interviews on four occasions (baseline, 2-4 days, 1-2 weeks, and 1 month after enrollment), 3) patient-completed paper medication diary for 10 days after enrollment, 4) Illinois Prescription Monitoring Program, 5) provider surveys, and 6) cost analysis from staff timesheets of build/maintenance of program.

4.C. Intervention: The ED EMC^2 Opioid Strategy comprised five changes to the EHR that were automatically triggered when any prescription for hydrocodone-acetaminophen was signed electronically. The first three components targeted providers, whereas the latter two components targeted the patient directly. The three prescriber-facing components were 1) a provider medication alert reminding the prescribing ED physician to counsel the patient about the safe use of opioids; 2) an inbox message delivered to the primary care outpatient provider informing them of the new prescription and pill quantity and requesting that they follow up with the patient to provide additional counseling about safe use; and 3) a request to the dispensing pharmacist to counsel the patient about safe use (printed automatically on the paper prescription requisition). In the event that there was no primary care outpatient provider, the inbox message was not able to be sent; however, the other two provider-facing components applied to all patients. The last two components of the ED EMC^2 Opioid Strategy, both patient facing, were plain language MedSheets about hydrocodone-acetaminophen and "Take-Wait-Stop" patient-centered medication labeling changes made to the print prescription requisition.

Figure 1: The ED EMC^2 Opioid Strategy Components and Flow Diagram



The MedSheets were previously developed by our team to provide the patient with understandable, actionable information written at an 8th grade reading level or below and formatted to result in higher recall of drug information compared with current FDA-standard Medication Guides. Preliminary data demonstrated that inclusion of an opioid MedSheet in ED discharge instructions increased some aspects of patient knowledge.



The Take-Wait-Stop prescription wording translates medications prescribed "as needed" into plain language with three deconstructed, actionable steps. The Take-Wait-Stop label was first developed by members of our team as an extension of the Universal Medication Schedule and is based on tenets of patient-centered prescription label design. The prescription wording places emphasis on action terms ("Take-Wait-Stop") and deconstructs the components of PRN instructions to support understanding and recall. Anticipating that the wording would be unfamiliar to community pharmacists, we additionally worked with a national community pharmacy chain manager to ensure that the wording fit on a standard label. Furthermore, the default *Sig* (i.e., *signetur*, which is Latin for "let it be labeled") on the print requisitions was changed to "Special Sig," and each prescription contained a "Note to Pharmacist: Please print the 'Take-Wait-Stop' instructions on the medication label" to draw attention to the wording change. This study was a pragmatic trial, so we did not ensure that each pharmacy could print the prescriptions, but we had a planned analysis of prescription bottle implementation.

The sixth component of the intervention, only available to patients in the EMC^2+SMS study arm, was SMS text messaging. Patients in this arm followed instructions on a pre-printed card and self enrolled into an automated texting program that sent one text message per day to the patients for the week following enrollment. These educational messages focused on safe use, side effects, and safe behaviors related to prescription opioids.

4. D. Measures:

Main analysis: The primary outcome was the patients' ability to safely dose their opioid medication in a "demonstrated" dosing task. As part of this task, patients were asked to tell the RA how they would take their medication if they were in pain ("starting at 8 am"). Participants were continually prompted as to when and how they would take their next dose if they were still in pain, with prompting continuing until either 24 hours was reached or the patient reported that they would not take any additional pills. Three error types were assessed in a binary fashion: proper number of pills per dose, correct spacing of doses (recommended minimum number of hours between doses), and total pills per day (not exceeding the recommended/safe number of pills per day). As the prescription details varied from patient to patient, each individual's compliance was assessed according to the wording of their prescription at discharge. For patients who did not have a "do not exceed' statement on their prescription, the manufacturer's recommendation was used (eight tabs daily for hydrocodone/ acetaminophen at the 5/325 mg strength and six tabs daily for the 10/325 mg strength). Each error type was reported separately and in aggregate, with the primary outcome being the aggregate assessment. Secondary outcomes assessed included medication knowledge and actual safe hydrocodone-acetaminophen use as assessed from medication diaries.

Implementation analysis: The study was conducted as a pragmatic trial to assess how the intervention would operate in the real world if it were "turned on" and then left to run without interference or repeated instruction. We measured the rate of successful printing of the MedSheet, the prescription requisition printing with the Take-Wait-Stop instructions, commercial pharmacies filling the pill bottles per the Take-Wait-Stop directions, and successful enrollment in the texting platform. We additionally conducted a pre- and post-sociotechnical system analysis in order to understand the ED and the system elements that impacted the effectiveness the EMC^2 strategy. Sociotechnical systems modeling illustrates the complexity of designing interventions for emergency medicine that affect multiple patients, providers, work systems, technologies, and processes.

Cost analysis: We also evaluated the cost of building the EHR customization and the cost of maintaining the system. Inputs included cost to reprogram the EHR, staff time to have patients self enroll in texting, cost of text messages, and program maintenance.

Acceptability: Finally, the EM physicians and APPs involved in the trial were anonymously surveyed to measure their counseling practices in the setting of the intervention and to obtain feedback on the intervention. For analysis of the provider survey, the two intervention arms were combined, as the provider-facing components of the intervention were identical between the two intervention arms.

4. E. Limitations: Patients were recruited from a single site in an urban area with a patient population that was relatively well educated and earned high income, limiting generalizability. Due to the study design and delivery of the intervention, patients needed to be consented after randomization, introducing selection bias.

Additionally, the study met with several recruitment challenges that we have detailed in Table 4 along with steps taken to improve recruitment, retention, and medication diary return. Although overall recruitment and retention did improve, some of the changes, including the switch from in-person to telephone interview, may have influenced measurement. Despite these attempts to improve recruitment, ultimately, the biggest limitation of the study was the sample size not reaching the planned enrollment target. In addition to the recruitment and retention challenges noted above, we had a low rate of return of the medication diaries, limiting generalizability from that data source.

An additional limitation is the use of dose demonstration as the primary outcome. Demonstrated dosing is an abstraction of actual dosing; compared with the medication diary dosing, our data show that the demonstrated dosing overestimates use and errors. This overestimation was anticipated based on our prior work; however, we opted to use the demonstrated dosing outcome, because prompting the patient to take the medications maximally for a 24-hour "day" uncovers label misunderstanding that is not readily apparent when patients are dosing their medication less frequently. Furthermore, the pragmatic nature limited outrcontrol over what was actually printed on the prescription bottles at the commercial pharmacies.

5. Results

5.A. Principal Findings:

Main analysis: The EMC^2 tools improved demonstrated safe dosing, but these benefits did not translate into actual safe use based on medication dairies. The SMS text-messaging portion of the intervention did result in improved patient knowledge.
Implementation Analysis: The portions of the intervention implemented at the health system level had high fidelity; however, the translation of the TWS label onto the pill bottle at the commercial pharmacies was low.
Cost Analysis: The intervention was low cost to build and maintain.
Acceptability: The intervention was well liked by physicians, who felt it had minimal workflow interruption; however, they did not often use the MedSheet or TWS prescription to counsel their patients.

5.B. Outcomes: Among 126 providers at the study site, 116 (92%) consented and were eligible for their patients to be enrolled. In total, 652 patients were enrolled in this study, for an overall cooperation rate of 57% of those approached (n=1,144). At the first follow-up call (2-4 days), retention rates were 67.3%, 74.1%, and 69.1% in the usual care, EMC^2, and EMC^2+SMS groups, respectively. The primary outcome was assessed at the second timepoint (1-2 weeks post enrollment); at that time, the retention rates were 47.0%, 58.0%, and 51.7%, respectively (Figure 1).

Demographic characteristics were well balanced between study arms. Recruitment included AHRQ priority populations, as shown in Table 1; 57% of the sample was female, 52% of the sample reported as racial/ethnic minorities (exceeding the estimated 50% in our planned enrollment table), 30% earned <$40,000/year, and 33% had low or marginal health literacy.

Main analysis: Overall, 76.4% of patients demonstrated safe use of their newly prescribed opioid, with the highest rate of safe use in the EMC^2 study arm (82.0%). Demonstrated safe use occurred more often in the EMC^2-alone group (adjusted odds ratio [aOR], 2.46; 95% CI, 1.19, 5.06), but not the EMC^2+SMS group (aOR, 1.87; 95% CI, 0.90, 3.90), compared with usual care. Less than half (39.8%, n=260) of patients returned medication diaries. There were no differences between arms in actual safe opioid use, as measured by medication diary data (Table 2). Participants in the usual care arm had the highest rates of concomitant use of sedating medications (30.7%) compared with the EMC^2 and EMC^2+SMS arms (21.0% and 25.9%, respectively); this difference was not statistically significant (Table 2). The most frequently used class of sedating medication was benzodiazepine (13.1%).

Patients in the EMC^2+SMS text-messaging intervention had higher composite knowledge scores (mean [SD], 6.2 [1.7); beta [95% CI], 0.57 [0.09, 1.06]) than participants in the usual care (mean [SD], 5.6 [1.5]) or EMC^2 arms (5.6 [1.8]). Specifically evaluating the strength of the deconstructed components of the intervention (EMC^2 arm versus EMC^2+SMS arm) revealed that the text messages were significantly linked to three knowledge items (able to name acetaminophen as ingredient, aware of need to avoid acetaminophen, aware of need to avoid sedating medications) (Table 3).

For all patients combined, patient report of counseling in the ED was high for medication name and indication (90.7% and 95.3%, respectively) but was much lower for other topics, including duration of use (44.3%), side effects (49%), directions for use (45.2%), and medications to avoid (33.8%), and did not differ significantly by study arm (data not shown). Despite the variable thoroughness of counseling, 91% of patients reported that they were highly satisfied with the counseling received (no difference by arm).

Implementation Analysis: The processes that occurred at the time of the ED visit had a high level of successful inclusion in the discharge documents, with 78% of patients in the intervention arms receiving printed MedSheets automatically (91% ultimately received the MedSheet after it was noted to be missing and the discharge documents were reprinted). Of the 248 patients in the intervention arms, 154 (62%) responded that they still had their information sheet 1-2 weeks post-visit. Additionally, 94 patients read the sheet again after they returned home from the emergency room. Within the EMC^2+SMS arm, 93% of patients successfully enrolled in texts. Only 19 patients (10%) opted out of the text intervention before all seven messages were delivered.

Although the Take-Wait-Stop prescription requisition successfully printed in the ED for 95% of patients in the intervention arm, this success did not translate to the patient due to variable implementation at the community pharmacy level. Upon follow-up, prescriptions labels were classified into three categories: (1) 1-step wording (Take 1 pill every 4 hours [*without* daily limits]); (2) 2-step wording (Take 1 pill every 4 hours, do not exceed 6 pills/day); and (3) 3-step wording. There were three subtypes of the 3-step wording: (a) 3-step, not TWS (three deconstructed steps, not necessarily TWS verbiage); (b) TWS format, employing three steps with leading verbs but "with additions or replacements" (e.g., replaced "do not take" with "do not exceed"); and (c) verbatim TWS.

In total, 211 participants had pill bottles available for analysis at follow-up. Bottles with 1-step wording represented 12% (n=25) of the sample, whereas 26% (n=55) had 2-step wording. The majority (44%, n=93) had three deconstructed steps, not TWS (a); 16% (n=34) retained TWS structure but not verbatim (b). Only 2% (n=4) displayed verbatim TWS wording (c). All category-3 labels (utilizing deconstructed instructions) were considered adequate implementation (62%). In contrast, 96.4% of control arm patients had labels with traditional PRN wording. Thus, although the TWS wording was not implemented verbatim, there was a moderate level of "adequate" implementation and significant change compared with the usual care arm.

The post-work systems analysis model illustrated that several elements in the external emergency department environment can affect the effectiveness of the intervention. These include physical changes to the department (e.g., new patient flow model changed how discharges were completed, and new locations of printers within the department) and work system changes (new process for writing prescriptions on tamper-proof paper resulted in running out of paper and prescriptions reverting to being written by hand).

Acceptability: Overall, 83 providers responded to the survey after completion of patient enrollment (25 in the usual care arm; 58 in the intervention arms). The EPs and APPs who were in the intervention arms self reported more frequently (very often or always) counseling patients about dosing instructions (70% in intervention arms versus 40% in control arm, p=0.01) and to avoid sedating medications (59.6% in intervention arm versus 33.3% in control arm, p=0.03). Otherwise, there were no differences in provider report of counseling. Most intervention arm providers liked the intervention and found it simple to use and not disruptive; however, only 22% of the providers surveyed reported regularly reviewing the contents of the MedSheet with their patients, and only 14% reviewed the Take-Wait-Stop wording of the prescription with their patients.

Cost Analysis The intervention cost $12,104 to build, with the majority of the expense coming from programming time related to the Take-Wait-Stop component of the intervention. The cost to maintain the SMS texting component was $140 over the course of the study, which equates to ~$0.40 per patient.

Additional Exploratory Analyses*:* In addition to the planned subanalyses, while conducting the study we encountered several additional interesting findings that prompted unplanned subanalyses:

1) A change of follow-up from in-person to telephone due to low retention enabled us to perform an analysis of how the NVS literacy measure performed via telephone and as a repeat measure.
    - Data from 216 patients (70 completing follow-up in person and 146 via telephone) were included. Reliability was high (ICCs: in-person=0.81, phone=0.70). Agreement was lower for the three-category NVS score (kappas: in-person=0.58, 95% CI [0.39-0.77]; phone=0.52, 95% CI [0.39-

0.65]) compared with two-category NVS (kappas: in-person=0.65, 95% CI [0.46-0.85]; phone=0.64, 95% CI [0.51- 0.78]).
- Correlations decreased as time between administrations increased. Internal consistency was moderately high (baseline NVS in person [α = 0.76], follow-up NVS in person [α = 0.76], and phone follow-up [α = 0.78]).
- The test-retest properties of the NVS are similar by mode of administration, suggesting that the NVS measure is reliably administered by telephone.

2) Qualitative data related to patient reasons for keeping their unused opioids prompted a mixed-methods manuscript evaluating the themes related to pill retention.
   - Patients were asked about their plans for their unused opioids. Responses were categorized as "dispose," "keep," and "don't know." Baseline characteristics were compared between the "keep" and "dispose" groups. Verbatim responses categorized as "keep" were analyzed qualitatively using a team-based inductive approach with constant comparison across cases.
   - One hundred patients planned to dispose of their pills; 117 planned to keep them. There were no differences in demographics between the groups; however, those in exposed to the intervention arm were more likely to plan to dispose (intervention arms combined, 80%; usual care arm, 66.7%; p=0.03).
   - Analysis revealed four categories of patient responses: 1) plans to keep their pills "just in case," with reference to a medical condition (e.g., kidney stone); 2) plans to keep pills "just in case" without reference to any medical condition; 3) plans to dispose in delayed fashion (e.g., after pill expiration) or unsure of how to dispose; and 4) no identified plans, yet intended to keep pills.
   - The intervention increased the odds of participants planning to dispose of their pills. Furthermore, an enhanced awareness of the range of motivations patient cite for keeping their pills may inform the development of tailored education and risk communication messages to improve opioid disposal.

3) Interview data related to patient understanding of "signs of addiction" prompted a qualitative analysis using a mixed inductive and deductive approach to evaluate how well patient understanding of signs of addiction mapped to the medical definition via DSM criteria.
   - During a follow-up interview, participants were asked, "What are the signs of addiction to pain medicine?" Verbatim transcribed answers were analyzed using a combined deductive and inductive team-based approach with content analysis and constant comparison. The initial codebook was based on Diagnostic and Statistical Manual of Mental Disorders V (DSM V) criteria for addiction; additional codes were identified in the coding process, with themes determined by consensus.
   - Overall, 325 participants responded to this question; 14 de novo codes were added to the 11 DSM V criteria codes, resulting in a framework of six themes. Participants reported that 1) effort spent acquiring opioids is a sign of addiction *("doing anything to get more tablets")* and 2) emotional and physical changes related to opioid use would be visible *("their eyes are different").* 3) Taking opioids when *"not needed,"* was frequently noted, including to *"get high," "to function,"* and for other indications such as sleep. 4) Increasing opioid use *("take more than prescribed")*, and the 5) inability to stop opioid use (*"can't stop taking it")* were additional participant-reported perceived signs of addiction. Finally, 6) an emotional relationship to opioids was viewed as a sign of addiction *("that you feel absent without it")*.
   - Many patient perceptions of signs of addiction were grounded in behaviors similar to concepts of addiction identified in DSM V. However, participants did have some misconceptions, omissions, and conflations of abuse behaviors with signs of addiction. Identifying and understanding these misconceptions will help inform patient-provider communication and future public health campaigns.

4) The granularity of the medication diary data has allowed us to help better characterize how patients are taking their pain medications after an ED visit for different painful conductions. This manuscript may help inform the quantity of pills that are prescribed by condition in the future.
   - Patients were included in this analysis if they returned the completed medication diary and had a discharge diagnosis in one of four categories: back pain, kidney stone, fracture, or

musculoskeletal injury (non-fracture). Opioid consumption is described using daily number of pills consumed and daily morphine milligram equivalents (MMEs) both for the sample overall and by diagnosis group. Additionally, the proportion of patients continuing opioid use is reported by post-visit day both overall and by diagnosis.

- In total, 191 patients with the diagnoses listed above returned completed medication diaries (45 [24%]) back pain, 52 kidney stone [27%], 54 fracture [28%], 40 [21%] musculoskeletal injury [non-fracture]). Pain scores on ED presentation were high and remained high after discharge (e.g., day 1: 7 [N=161], day 2: 7 [N=143], day 3: 6 [N=122]). The mean quantity of opioid pills prescribed was 16 tabs.
- On the day of discharge (day 1), 85% of patients consumed an opioid at home (87% back pain, 73% kidney stone, 93% fracture, 88% musculoskeletal injury) with mean tablets consumed of 1.7 (SD, 1), resulting in 11.2 (7.9) MME (13.9 [11.4] MME back pain, 9.5 [5.2] MME kidney stone, 10.7 [6.9] MME fracture, 11.1 [6.6] MME musculoskeletal injury). The proportion of patients consuming opioids on subsequent days decreased on the day after discharge for patients with kidney stones (42%) and fractures (81%), remained stable for those with musculoskeletal pain (90%), and increased for those with back pain (91%). Among those patients taking pills on the first 2 days after discharge (days 2 and 3), the MME consumed increased (15 [10.2] and 15.6 [12.2] MME, respectively) before decreasing on subsequent days (day 4: 13.5 [11.5] MME; day 5 13.3 [9.2] MME).
- Only 7.7% of patients with kidney stones consumed more than 12 pills; conversely, 42.2% of those with back pain consumed more than 12 pills in the 10 days after discharge. Overall, 81% of patients had leftover pills (66% back pain, 96% kidney stones, 74% fracture, 87% musculoskeletal injury).
- In this sample, pill consumption varied by illness category; however, patients overall were consuming low quantities of pills, and the majority had unused pills 10 days after their ED visit. Additional data could help support prescribing tailored by diagnosis and minimize unused pills.

5.C. Discussion: The ED EMC^2 Opioid Strategy had some significant, but overall variable, influence on the outcomes studied. In the demonstrated use condition, the EMC^2 intervention led to higher rates of safe use; however, this success did not translate into actual safe use as measured by the medication diaries. Despite the lack of difference in the actual use condition, the success of the intervention in the demonstrated use scenario supports the value of the EMC^2 intervention and specifically the Take-Wait-Stop label, which was the portion of the intervention with the highest likelihood of influencing the dosing outcome.

Patients in the EMC^2+SMS arm had higher composite knowledge scores than patients in the usual care arm and the EMC^2 arms, supporting the use of SMS text message delivery after the visit to reinforce safe use. Although the score was higher, it is unclear if this finding is clinically meaningful. However, examining the component parts of the score, patients had higher levels of knowledge about the need to avoid both sedating medications and acetaminophen. These two knowledge items are arguably among the most important, because co-ingestion of opioids with both sedating medications and acetaminophen are linked to mortality.

The success of the SMS text portion of the intervention to impart knowledge is one of several recent examples of extending the reach of emergency care into the post-visit time period through technology (text messaging, mobile applications, telehealth), a growing and promising avenue for behavioral interventions. Technology-based health interventions in the ED have been steadily growing and expanding from interventions delivered within the confines of the visit to mobile health interventions delivered post-visit. In the context of pain management and analgesics (not specifically targeting opioid use disorder), few studies have been published. We believe that technology-delivered interventions such EMC^2+SMS have great potential in the context of pain management, not only because of their reach into the post-visit space, wherein the patient is less distracted, but also because the interventions are scalable and can be delivered at the time of the behavior being targeted.

The patients in the EMC^2+SMS arm were also more likely to plan to dispose of their pills than were those in the other study arms. Disposal of unused opioids continues to garner attention as one major lever by which to decrease opioid abuse, because a majority of misused opioids are obtained from friends or family members. A better awareness of why patient are opting to keep the opioid pills will help to inform future interventions.

Along with the potential benefits described above, the text messaging was inexpensive and well tolerated by patients, with only a very small minority opting out of the messages. Patients enrolled themselves

into the texting, supporting its acceptability. In addition to being well tolerated by patients, the intervention was also well received by physicians. The anonymous feedback on the intervention was overall positive and showed that it was not intrusive to workflow. However, the providers did not routinely use the patient-facing components (e.g., MedSheet and TWS Prescription) to help guide their discharge conversation and rarely reviewed the materials with the patients, perhaps contributing to the lack of effect of the EMC^2 portion of the intervention with respect to the knowledge items.

5.D. Conclusions: We found that the intervention improved demonstrated safe dosing of opioids and increased patient knowledge while being simultaneously low cost with minimal workflow interruption; however, we were not able to demonstrate a significant impact of the intervention on patients' actual safe use of their medications. This lack of impact may have been partly due to the low frequency of "maximal dosing" of the medications at home (versus the demonstrated dosing task that prompts more maximal dosing) or related to the fidelity with which the TWS bottles were filled in the community pharmacies. We additionally found that the SMS portion of the intervention was possibly the most powerful for imparting knowledge, with patients receiving the messages having higher odds of planning to dispose of their pills and awareness of use precautions related to Tylenol and benzodiazepines. Though we do not discount the importance of the communication at the bedside, future interventions may opt to focus on post-discharge follow-up communication with ED patients, as the greatest increases in knowledge in this sample were seen among patients receiving the text-messaging portion of the intervention.

In addition to documenting effect of the intervention, this grant has further generated a greater understanding of 1) the use of a common health literacy measurement tool, 2) understanding of why patients keep their unused opioids, 3) understanding of what patients think are "signs of addiction," 4) how pharmacies implement changes in prescription wording, and 5) how many pills patients use after an ED visit for acute pain.

5.E. Significance and Implications

Although the cost of the EHR build was relatively low, additional cost would be needed to customize it to all opioids rather than to only hydrocodone. Despite its value in improving demonstrated use, given the relatively low impact of many of the embedded portions of the intervention on actual use, we were advised by our dissemination advisory panel that the full suite of EMC^2 tools may not be ready for widespread dissemination. However, the data do support continued study and implementation of the TWS label to improve safe dosing of PRN medications. Although the label was not implemented with high fidelity, the changes that were made resulted in an improvement of medication dosing in the demonstrated use condition compared with usual care. These benefits would more likely translate to differences in actual use among patients taking the medication with higher frequency (e.g., patient with chronic pain or cancer) or with other PRN medications (anxiolytics, over-the-counter cough/cold medications).

This study also highlights the importance of studying implementation measures in pragmatic trials. Although a high proportion of patients received the intervention at the health system level, for the intervention component involving commercial pharmacies, there was very low implementation fidelity. Multiple groups, including the National Academies of Medicine and the Food and Drug Administration, are continuing to discuss ways to improve drug labeling and information provided to consumers. These findings underscore the importance of any of their forthcoming recommendations being implemented on a state or national scale, supported by legislation, rather than being in the format of recommendations to providers or dispensers. Due to the low levels of accurate implementation of the TWS label, it is difficult to assess its true impact on medication dosing in actual use, and further study is planned.

Additional implications for this work included bolstering the evidence for the use of mobile technologies to impart information to patients after an ED visit. The SMS portion of the intervention was the most successful portion for imparting knowledge to patients. This use aligns with a growing number of publications on the use of mobile technologies for behavioral health interventions after an ED visit, but it is the first use of text messaging in the context of opioid knowledge of which we are aware. We have disseminated our text messages in the publication of the main results manuscript (under revision with Academic Emergency Medicine) and plan future revision of the messages to determine why half of the items resulted in knowledge/behavior change but the other items did not.

6. **List of Publications and Products**

1. McCarthy DM, Courtney DM, Lank PM, Cameron KA, Russell AM, Curtis LM, et al. Electronic medication complete communication strategy for opioid prescriptions in the emergency department: Rationale and design for a three-arm provider randomized trial. Contemp Clin Trials. 2017;59:22-9.

2. Russell AM, Patel DA, Curtis LM, Kim KA, Wolf MS, Rowland ME, et al. Test-retest reliability of the Newest Vital Sign health literacy instrument: In-person and remote administration. Patient education and counseling. 2019;102(4):749-52.

3. Neill LA, Kim HS, Cameron KA, Lank PM, Patel DA, Hur SI, et al. Who Is Keeping Their Unused Opioids and Why? Pain Med. 2019. [epub ahead of print]

4. McCarthy DM, Russell AM, Eifler MR, Opsasnick LA, Lyden AE, Gravenor SJ, et al. Implementation Fidelity of Patient-Centered Prescription Label to Promote Opioid Safe Use. Pharmacoepidemiology and Drug Safety. (*in press*)

5. Montague E, Bungum M, Sherman L, Gravenor S, Courtney DM, Czerniak A, et al. A system analysis of an intervention to improve opioid prescribing in emergency medicine. Applied Ergonomics. *(under revision).*

6. McCarthy DM, Curtis LM, Courtney DM, Cameron KA, Lank PM, Kim HS, et al. A multi-faceted intervention to improve patient knowledge and safe use of opioids: Results of the ED EMC^2 randomized controlled trial. Academic Emergency Medicine (*under revision*).

7. McCarthy DM, Kim HS, Lank PM, Arroyo C, Hur SI, Opsasnick LA et al. Opioid pill consumption after an ED visit: How many pills are people using? *in preparation targeting Annals of Emergency Medicine (likely submission July 2019)*

8. Serina PT, Lank PM, Kim HS, Courtney DM, Opsasnick LA, Curtis LM, et al. Perceptions of signs of addiction among patients prescribed opioids in the ED. *in preparation targeting Journal of Addiction Medicine (likely submission June 2019)*

Figure 1: Consort Diagram

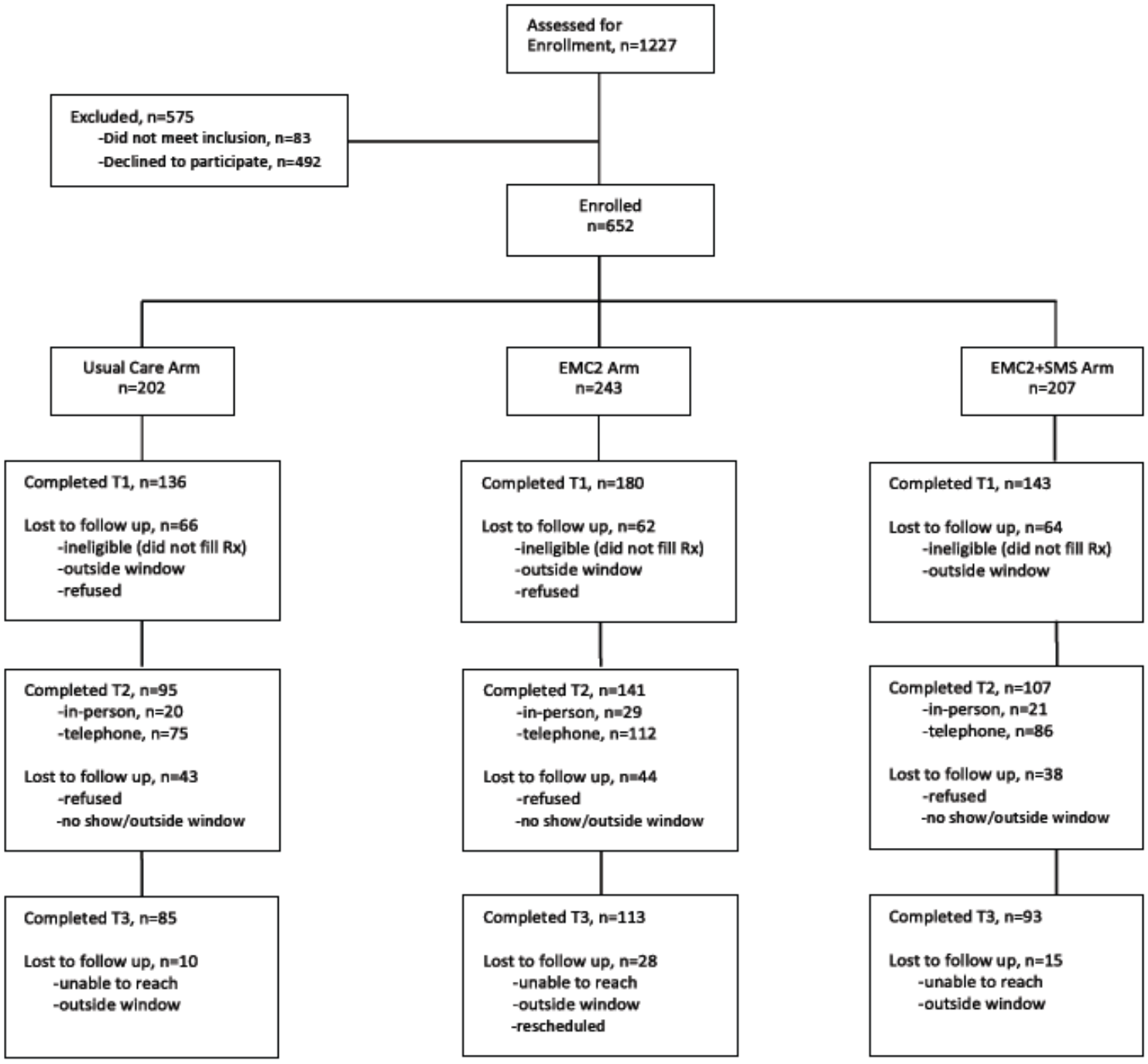


Table 1: Participant Demographic Characteristics Overall and by Study Arm

Characteristic		Usual Care Arm n=202	EMC² Intervention Arm n=243	EMC²+SMS Intervention Arm n=207
Demographic Characteristics				
Age, *mean years (SD)*	42.2 (14.0)	43.3 (14.2)	42.3 (14.4)	41.3 (13.3)
Female gender, *%*	57.1	55.9	55.6	59.9
Race, *%*				
White	46.9	47.3	45.5	48.3
African American	30.8	32.8	29.3	30.4
Other	22.3	19.9	25.2	21.3
Education, *%*				
High school grad or less	18.0	17.3	18.1	18.4
Some college	31.8	34.7	31.3	29.6
College graduate	31.3	26.2	33.7	33.5
Graduate degree	18.9	21.8	16.9	18.4
Income Level, *%*				
<=$40,000	30.6	32.6	30.9	28.0
>$40,000-$100,000	34.7	37.0	35.0	32.0
>$100,000	34.7	30.4	34.1	40.0
Health Literacy, *%*				
Low+Marginal	33.6	35.1	32.9	32.9
Adequate	66.4	64.9	67.1	67.1
Primary Insurance, *%*				
Medicaid	18.0	17.9	19.2	16.7
Medicare	7.6	10.9	6.3	5.9
Private/Managed Care	63.5	58.7	65.7	65.5
Self or no insurance	6.4	6.5	5.9	6.9
Other	4.5	6.0	2.9	4.9

Table 2: Outcome Measures by Study Arm

	Usual Care Arm %	EMC² Arm %	EMC²+SMS Arm %	EMC² vs. Usual Care Adjusted Model Outcome aOR (95% CI)	EMC²+SMS vs. Usual Care Adjusted Model Outcome aOR (95% CI)
PRIMARY SAFE USE OUTCOME					
Outcome of Demonstrated Dosing Activity					
Exceeded maximum daily dose	1.2	6.5	3.1	--	--
More than prescribed pills per dose	3.6	4.0	2.0	--	--
Shorter interval than prescribed	26.6	15.6	22.9	--	--
Demonstrated Safe Use (no errors)[a]	68.4	82.0	76.0	2.46 (1.19, 5.06)*	1.87 (0.90, 3.90)
SECONDARY SAFE USE OUTCOMES					
Actual Use based on Medication Diary *(N=260)*					
Exceeded maximum daily dose	1.3	2.0	0.0	--	--
More than prescribed pills per dose	10.7	8.0	7.4	--	--
Shorter interval than prescribed	9.3	10.0	5.9	--	--
Use with sedating medication	37.3	24.0	28.2	--	--
Actual Safe Use (no errors)[b]	52.0	67.0	65.9	1.82 (0.95, 3.48)	1.75 (0.89, 3.44)
KNOWLEDGE				**Beta (95% CI)**	**Beta (95% CI)**
Knowledge Composite Score, Mean (SD)[c]	5.6 (1.5)	5.6 (1.8)	6.2 (1.7)	-0.02 (-0.47, 0.42)	0.57 (0.09, 1.06)*

aOR: adjusted Odds Ratio

[a] adjusted for health literacy and clustering

[b] adjusted for clustering

[c] adjusted for race, income, health literacy, and clustering

[+] Indicates questions that were part of the text message

Table 3: Outcome Measures – By Intervention Component		
	Texting vs. EMC[2]	
	aOR (95% CI)	**P value**
PRIMARY SAFE USE OUTCOME		
Demonstrated Safe Use[a]	0.81 (0.36, 1.82)	0.60
SECONDARY SAFE USE OUTCOME		
Actual Safe Use based on Medication Diary+[b]	0.71 (0.35, 1.46)	0.35
KNOWLEDGE[c]		
Knowledge of Medication Details (N=459)		
Able to identify by brand name	1.70 (0.82, 3.49)	0.15
Able to name acetaminophen as an active ingredient+	2.46 (1.16, 5.22)	**0.02**
Able to name hydrocodone as an active ingredient	1.26 (0.66, 2.39)	0.49
Aware that medication is a narcotic/controlled substance	0.82 (0.38, 1.78)	0.62
Awareness of Precautions (N=343)		
Aware of safe amount of alcohol to drink+	0.88 (0.38, 2.04)	0.77
Aware of need to avoid other sedating medicines+	2.17 (1.20, 3.91)	**0.01**
Aware that prescribed medication can be addictive	0.57 (0.25, 1.29)	0.18
Aware that you should avoid acetaminophen+	2.72 (1.49, 4.96)	**0.001**
Side Effects (N=343)		
Recognized at least one GI side effect (vomiting, nausea, constipation) +	1.28 (0.69, 2.35)	0.43
Recognized at least one sedating side effect (sleepy, dizzy, tired)	1.01 (0.58, 1.74)	0.98
	Beta (95% CI)	
Knowledge Composite Score[c]	0.61 (0.13, 1.08)	**0.014**

aOR: adjusted Odds Ratio

[a] adjusted for health literacy and clustering

[b] adjusted for clustering

[c] adjusted for race, income, health literacy, and clustering

+ Indicates questions that were part of the text message

Table 4: Recruitment Challenges and Strategies Implemented	
Challenges	**Strategies Implemented**
Opioid prescription rates lower than historical numbers	Decreased rates of prescription of opioids from the ED resulting in fewer eligible patients, particularly during daytime hours. Study designed in 2014 and, at that time, ~16% of ED discharges from site received Norco. By the end of the study in August 2017, ~7-8% of ED discharges from site receive an opioid. • RA recruitment in evening hours • Study information reminders to physicians via email and on daily RA recruitment rounds at time of sign out
Overall low recruitment	Staffing issues related to RA on leave followed by two RAs departing for other employment • Replaced with new hires • Follow-up calls moved to off-site, non-screening RAs to allow ED RAs more recruitment time
Patient declining to do screener	Thought to be due to patients eagerness to leave at end of long ED visit and unwilling to stay for 5-10 minute consent and baseline interview • Approach patients earlier in visit once identified by provider as having an anticipated discharge with new opioid prescription • IRB approved flyer to notify patients of study earlier in visit • RAs introduced by treating physician
Screened and eligible patients declining study participation	Thought to be due intensity of follow-up • Switched 7-14 day interview from in person to by telephone
Low follow-up rates of consented patients and low rate of medication diary return	• Changed incentive structure (total compensation remained stable) from enrollment: $10, in-person visit: $25 to enrollment: $5, 2-4 day call: $10, 7-14 day call & medication diary return: $20
Slower rate of patient accrual than anticipated	• Recruitment period extended an additional 6 months