

Oxycodone Ingestion Patterns in Acute Fracture Pain With Digital Pills

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BACKGROUND: Opioid analgesics are commonly prescribed on an as-needed (PRN) basis for acute painful conditions. Uncertainty of how patients actually take PRN opioids, coupled with a desire to completely cover pain, leads to variable and overly generous opioid prescribing practices, resulting in a surplus of opioids. This opioid surplus becomes a source for diversion and nonmedical opioid use. Understanding patterns of actual opioid ingestion after acute painful conditions can help clinicians counsel patients on safe opioid use, and allow timely recognition and intervention when escalating opioid self-dosing occurs, to prevent tolerance and addiction.

METHODS: We used a novel oxycodone digital pill system (ingestible biosensor within a standard gelatin capsule combined with 5-mg oxycodone) that when ingested, is activated by the chloride ion gradient in the stomach thereby emitting a radiofrequency signal captured by a wearable reader. The reader relays ingestion data to a cloud-based server that displays ingestion events to the study team. We deployed the oxycodone digital pill among opioid-naïve individuals discharged from the emergency department with acute fracture pain. Participants were trained on digital pill operation and discharged with twenty-one 5-mg oxycodone digital pills. They were instructed to take digital pills PRN for pain on discharge. We conducted a brief interview 7 days after study enrollment, at which point participants returned the digital pill system. We identified oxycodone ingestion events in real time by data from the digital pill system and performed pill counts at the return visit to validate digital pill reporting of medication ingestion.

RESULTS: In this study, 26 individuals were approached; 16 enrolled with 15 completing the study. Participants ingested a median of 6 (3–9.5) oxycodone digital pills over the course of 7 days, with 82% of the oxycodone dose ingested in the first 3 days. In individuals who required operative repair, 86% (N = 6) continued to ingest opioids at 1 week. There was substantial variability in ingestion patterns between individuals.

CONCLUSIONS: The utilization patterns of individuals with acute fracture pain could be captured using a digital pill system and revealed a median opioid ingestion of 45-mg morphine equivalents for acute pain over 7 days. Seven participants ceased using opioids within 4 days after discharge from the emergency department, although operative repair was associated with longer use. This digital pill system was able to measure changes in and patterns of opioid self-dosing, which varied between patients. (Anesth Analg 2017;125:2105–12)

KEY POINTS

- **Question:** How do discharged emergency department opioid-naïve patients take opioids prescribed on an as-needed basis after acute fracture pain?
- **Findings:** Using a digital pill medication ingestion monitor, emergency department patients ingested a median of 6 oxycodone digital pills in the 7 days after sustaining an acute fracture.
- **Meaning:** Opioid-naïve emergency department patients with acute fracture pain ingest less opioids over a shorter period of time than previously thought.

Opioids are commonly prescribed on an as-needed (PRN) basis, meaning that in the outpatient setting, patients make all decisions regarding opioid dose and frequency relatively independently, and not according to any predefined schedule. Data on how patients actually take PRN opioids (eg, the timing, number, and frequency of dosage units ingested) are unknown. Wide variation

exists in how clinicians prescribe opioids in response to acute pain, and providers often err on the side of too many to avoid the inconvenience of refilling prescriptions, a practice that contributes to excess opioid dosage units in the community.¹ Prior investigations suggest that 42%–72% of prescription opioids are left unused after outpatient surgical procedures.^{1–6} Although several investigations have

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demonstrated a large portion of prescribed opioids are unused, previously used methods consist of pill counts (often at a single timepoint), prohibiting any description of the patterns by which individuals ingest PRN opioids.

Current methods to measure medication ingestion are indirect; they rely on pill counts, pharmacy refills, Micro-Electro-Mechanical Systems caps that detect opening of pill bottles, patient diaries, and urine drug screens.⁷⁻⁹ Long-term opioid adherence monitoring uses urine or hair drug screening, methods that suffer from difficulty in interpretation, varying analytic techniques, and inaccurate results depending on the relationship between opioid ingestion and sample acquisition.^{10,11} These monitoring methods describe opioid use in aggregate, are easily manipulated, and fraught with user bias. Aggregate measures of opioid ingestion miss important dynamic information such as the dose per ingestion as well as changes in dosing interval. Real-time changes in dosing interval, or increased dose per ingestion, may indicate problems with pain control or important changes in the nature of opioid use, and thus represent an opportunity for assessment and early intervention—a phenomenon that is difficult to detect through current measures.

Digital pills—where a medication is incorporated into a gelatin capsule containing a biosensor that activates in the stomach—can provide direct and definitive evidence of medication ingestion.¹²⁻¹⁷ Iterative improvements in data transmission and signal strength have made digital pills feasible and acceptable to patients.¹³ Formative data on the use of digital pills have demonstrated the ability to detect ingestion of antidiabetic agents, antipsychotics, and anti-tuberculosis medications.^{14,18,19} Although used to measure medication adherence, direct ingestion monitoring through digital pills creates a new opportunity to measure more than just adherence. In the setting of opioid use, knowledge of real-time ingestion can produce relevant information regarding the opioid dose (number of pills ingested) as well as the timing interval between opioid ingestions. Patterns of escalating dosage or increased interval dosing or conversely, patterns of decreased dosing and tapering can help clinicians manage acute exacerbations of pain. In the present study, we report data on opioid ingestion patterns detected by a digital pill in emergency department (ED) patients discharged after treatment for acute fractures. We additionally report qualitative user acceptance of digital pills to monitor opioid ingestion patterns after acute fracture pain.

METHODS

Institutional Review Board and Patient Consent

This study was approved by our institutional review board; written informed consent was obtained from all study participants.

Digital Pill Technology

We utilized a digital pill system (eTectRx, Newbury, FL) (Figure 1) to measure opioid ingestion patterns. The digital pill system is an investigational device, classified by the Food and Drug Administration as a nonsignificant risk device. The digital pill comprises an ingestible radio-frequency emitter and a standard gelatin capsule sized to

accept a single 5-mg oxycodone tablet. Each oxycodone digital pill contains its own unique radiofrequency emitter. When the digital pill is ingested, the gelatin capsule is dissolved, liberating the oxycodone tablet. Chloride ions energize the ingestible radiofrequency emitter that transmits a unique signal containing ingestion time and preprogrammed pill identification number. This signal is acquired by a cutaneous patch adhered to the abdominal wall. The patch is attached by a cable to a reader (approximately the size of an iPod) that stores and relays ingestion data through cellular signaling to a cloud-based server that collates and displays ingestion events. On capturing the radiofrequency signal, the reader also sends a text message to the investigational staff and study participants confirming the ingestion event. The reader only needs 2–3 seconds to capture the transmitted signal from the digital pill. The digital pill has been utilized without evidence of retention of the radiofrequency transmitter in the gut, and no adverse events have been reported in previous safety trials.¹⁶ Digital pills were packaged in a standard blister pack; there was no particular order in which participants were required to take digital pills. A total of 21 dosage units (eg, twenty-one 5-mg oxycodone digital pills) were dispensed to each study participant.

Design

This manuscript adheres to the applicable transparent reporting of evaluations with nonrandomized designs (TREND) guidelines.²⁰ We performed a descriptive study of opioid-naïve adults discharged from a tertiary care ED between February 2016 and November 2016 with a diagnosis of acute fracture. We excluded individuals who had previous psychiatric and drug abuse histories, were admitted for fracture care, lived outside our catchment area and therefore would be unable to follow-up with us, or had multiple sites of injury. Trained research assistants (RAs) used the electronic medical record to screen ED patients for inclusion/exclusion criteria before approaching them for participation in the study. Eligible participants were approached in the ED and enrolled on a convenience basis pending the availability of the RA and an investigator. Participants were only able to be recruited during the times the investigational pharmacy was open (8 AM–5 PM, weekdays) as digital pill oxycodone was dispensed by our investigational pharmacy for this study. After providing written informed consent, participants before discharge received a 15-minute training session from the RA on the operation of the oxycodone digital pill before discharge. A study investigator (P.R.C., S.C., or E.W.B.) filled out a prescription for oxycodone digital pills for the hospital investigational pharmacy to dispense oxycodone digital pills to participants before their discharge from the ED. Participants then demonstrated use of each component; we verified successful use of the technology once participants had ingested the digital pill and received a text message confirming ingestion.

We instructed participants to use oxycodone (one to two 5-mg oxycodone digital pills every 6–8 hours) as needed for pain and ensured that study participants did not receive additional prescriptions for opioid analgesics at discharge from the ED, orthopedic services, or their primary care physician. Participants returned equipment and unused digital pills to

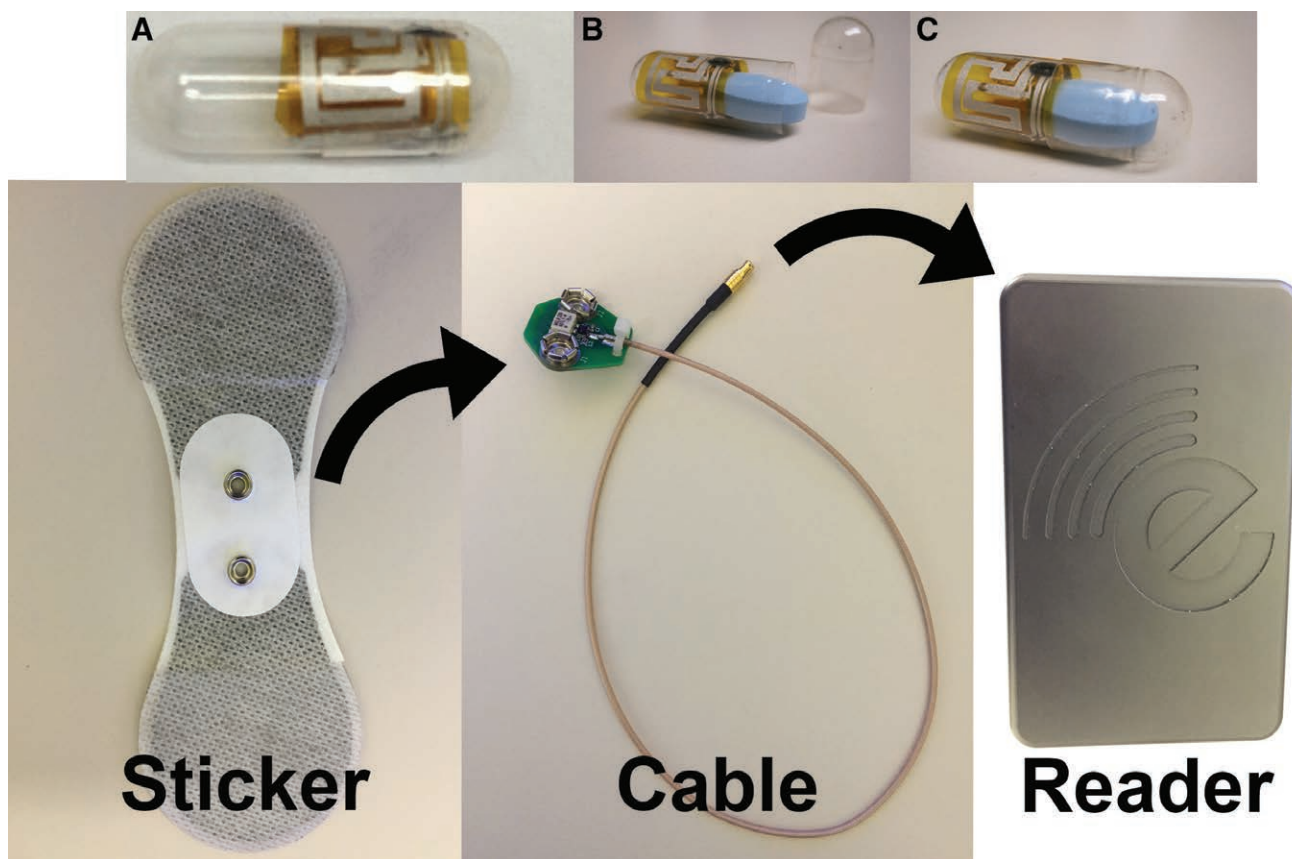


Figure 1. The digital pill comprised of an ingestible radiofrequency emitter combined with a gelatin capsule (A) sized to accept an oxycodone tablet (B) creating an oxycodone digital pill (C). The reader is composed of an adherent sticker attached by a cable to the reader that records ingestion events from the digital pill.

our clinical research center at the end of 7 days or at the time of their follow-up orthopedic clinic visit. During this visit, we reviewed ingestion data with participants and conducted a pill count to assess the validity of the digital pill measurement. We also asked participants about their subjective quality of pain control and their decision-making process regarding whether and when to taper oxycodone use. Participants were remunerated for their participation in the study.

Statistical Analysis

Oxycodone ingestions were measured by the digital pill system and collated on a Research Electronic Data Capture database. Results were downloaded, and basic descriptive statistics were calculated on Microsoft Excel (Redmond, WA). Ingestion of the oxycodone digital pill associated with system training in the ED was marked time as 0; the study period ran for the next 7 days from this timepoint. If a patient reported adequate pain management at the time of system training, time 0 for the study period was time of patient discharge. Ingestions were defined as taking place on day 1 if they were recorded between time 0 and 24 hours, day 2 from 25 to 48 hours, day 3 from 49 to 72 hours, etc. Ingestion of oxycodone digital pills was recorded for 7 days; we calculated dose amount and dosing interval using ingestion data downloaded from our study server.

Patients were prescribed one to two 5-mg oxycodone digital pills every 6 to 8 hours as needed for pain. We calculated dosing interval by dividing 24 hours by the average number

of doses taken in a day across all participants. A dose was defined as taking one or two 5-mg oxycodone digital pills at the same time. If a participant took two 5-mg oxycodone digital pills at 1 time, we considered that 1 dose of 10 mg. Because of the sample size, we calculated the median dose ingestion over the study period and median dose ingestions per day for the entire set of participants. We separated participants into those who required operative management of their fracture and those who were managed nonoperatively. We then calculated median ingestion amount and dosing interval for each group.

RESULTS

During the study period, 26 individuals were eligible and approached for the study (Figure 2). Ten individuals declined to participate; the majority of nonconsenting individuals reported that they preferred a different opioid formulation that we did not compound with the digital pill ($N = 2$), that they did not want opioids on discharge ($N = 2$), that they did not intend to participate in the follow-up interview ($N = 1$), or that they did not reside in our region ($N = 1$). None refused participation based on concerns related to ingesting a biosensor. There were no deviations from the study protocol. Of the 16 individuals consented, 15 completed the study. The 1 individual who did not complete the study reported that excessive pain prevented him from recharging the battery of the reader. The mean age of study participants was 45 years; 60% ($N = 9$) identified as

male, while 40% (N = 7) identified as female (Table 1). Seven participants ultimately required operative repair of their fracture, while 8 participants were treated nonoperatively.

The digital pill recorded a total of 112 ingestion events (Table 2); pill counts demonstrated a total of 134 ingestions (84% accuracy). All missed ingestion events were isolated to 2 study participants who ingested digital pills without wearing the reader, or did not recharge the reader due to severe pain. The digital pill system detected 34 simultaneous ingestion events where participants ingested 2 pills at 1 time. Eighteen of these episodes (52%) occurred in the first 48 hours after discharge.

Participants ingested a median of 6 (3–9) oxycodone digital pills (45-mg morphine equivalents) during the study period (Figure 3). The majority, 82%, of cumulative oxycodone doses per participant was ingested in the first 72 hours. After 3 days, 46% (N = 7) participants had stopped taking oxycodone. Most participants self-tapered their oxycodone dosing intervals over the first 72 hours after discharge (Figure 4). In the first 24 hours after discharge, participants ingested oxycodone digital pills on average every 12 hours, and then typically lengthened their dosing interval to 1 ingestion daily at 48 hours after discharge.

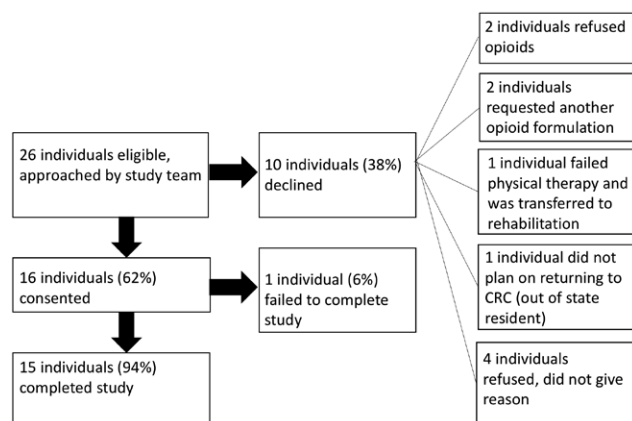


Figure 2. Study schematic and enrollment pattern. CRC indicates clinical research center.

Participants returned a mean of 12 oxycodone digital pills at the end of the study period.

Participants who required operative repair (N = 7) ingested a median of 8 (range: 6–11) oxycodone digital pills (60-mg morphine equivalents); 84% of the cumulative dose was ingested in the first 72 hours. Six of the 7 participants (86%) with operative fractures remained on oxycodone at 1 week, while 1 participant did not ingest opioids during the study period. Most participants with operative fractures ingested oxycodone digital pills every 8 hours for the first 24 hours before tapering down to every 24 hours at 48 hours after discharge.

Participants with nonoperative fractures (N = 8) ingested a median of 5 (range: 1.5–7) oxycodone digital pills (37.5-mg morphine equivalents); 80% of the cumulative dose was ingested in the first 72 hours. On average, participants ingested oxycodone digital pills once daily for the first 24 hours and had stopped taking oxycodone digital pills 96 hours after their injury. No participants who were managed nonoperatively continued to ingest opioids at the end of the study period.

Most participants (N = 12) self-reported that their pain was well controlled during the study. Ten participants (66%) reported pain that was severe (eg, in the range of 7–10/10), prompting them to use the oxycodone digital pill for the first 72 hours. Although most participants reported they continued to feel pain after 3 days, 10 reported that the intensity of pain had decreased until it was adequately managed with nonsteroidal antiinflammatory drugs and acetaminophen. Of note, 6 participants reported even after their pain had subsided, they continued to ingest oxycodone digital pills in the evening before bedtime as “prophylaxis” against potential episodes of pain in the morning.

DISCUSSION

The findings of this pilot study indicate that most opioid-naïve patients self-administer opioids to manage the pain from acute fracture for only a brief period, even among patients with fractures requiring surgical management. Furthermore, most patients stopped self-administering opioids in advance of exhausting their opioid supply. The point at which most of our patients completely stopped taking opioid analgesics after fracture, 96 hours, is far shorter

Table 1. Demographics, Fracture Pattern, and Final Treatment of Study Participants (N = 15)

Participant	Age (y)	Sex	Injury	Definitive Therapy
2002	32	M	Lisfranc fracture	Surgical fixation
2003	48	F	Distal radius ulna fracture	Surgical fixation
2004	55	M	Trimalleolar fracture	Surgical fixation
2005	55	M	Bimalleolar fracture	Surgical fixation
2006	63	F	Tibial plateau, proximal fibula fracture	Knee immobilizer
2007	21	M	C6 right pedicle fracture, L2+L3 transverse process fracture	Cervical collar
2008	44	F	Distal fibula fracture	Controlled ankle motion boot
2009	66	F	Distal fibula fracture	Short leg cast
2010	27	F	Distal fibula fracture	Short leg cast
2011	55	M	Distal radius fracture	Wrist splint
2012	21	F	Distal radius fracture, ulnar styloid fracture	Surgical fixation
2013	50	M	L3 superior endplate fracture	Thoracolumbar orthosis
2014	54	M	Calcaneal fracture	Surgical fixation
2015	55	M	Bimalleolar fracture	Surgical fixation
2016	55	F	Distal radius fracture	Wrist splint
2017	32	M	Lisfranc fracture	Surgical fixation

Abbreviations: F, female; M, male.

than the week-long duration of opioid analgesia for the management of acute pain often prescribed by physicians.^{5,6} In addition, we observed that the majority of participants, whether they had operative and nonoperative fractures, tapered (increasing the length of intervals in their dosing schedule) the dose of opioid analgesic. These findings therefore may be used to improve the precision with which physicians prescribe opioids. Rather than prescribing medications on a PRN basis, we propose that clinicians consider instructing patients to begin tapering the dose of opioid analgesics beginning at 24 hours after injury, which would also reduce the number of pills dispensed, and ultimately wasted or made available for diversion.

Table 2. Accuracy of the Digital Pill Recording Ingestion Events

Subject	Ingestion Events Recorded	Pills Taken (Based on Pill Count)	System Accuracy (%)
2002	16	16	100.00
2003	14	14	100.00
2004	14	20	70.00
2005	9	9	100.00
2007	16	16	100.00
2008	12	20	60.00
2009	6	6	100.00
2010	0	0	100.00
2011	2	2	100.00
2012	0	0	100.00
2013	8	8	100.00
2014	4	4	100.00
2015	5	13	38.46
2016	0	0	100.00
2017	6	6	100.00
Total	112	134	84

Interestingly, patients only ingested a median of 6 pills, despite being given 21 pills to each participant, suggesting that even a week-long duration of therapy after fracture may represent overprescribing opioids. Overprescribing may lead to several important problems. First, it may encourage increased opioid use by that patient. A recent study of post-operative patients showed an association between a larger number of tablets dispensed and the number consumed, independent of patient characteristics or pain, suggesting that patients may take more pills just because they are given more, and that this does not lead to improved pain control or satisfaction.^{21,22} Our results showing that most patients stopped use within 3 days are especially significant in light of data from the Centers for Disease Control and Prevention that correlate opioid therapy of >3 days duration with long-term nonmedical opioid use.^{23,24} Limiting the availability of unused opioids through evidence-based prescribing is an effective strategy in preventing downstream opioid abuse.²⁵

Investigators have proposed limiting the number of opioid dosage units to the amount truly needed for a specific clinical indication.^{26,27} Unfortunately, previous methods of assessing medication-taking behavior (which only infer but do not measure ingestion) are easily manipulated, suffer from user bias, provide aggregated information regarding opioid ingestion, and thus cannot provide information on patterns of opioid ingestion. Consequently, the precise number of dosage units and duration of therapy have remained undefined. Our data suggest that approximately six 5-mg oxycodone tablets, when properly tapered, may be sufficient to control pain from acute fractures in the majority of patients, and may serve to support governmental policies directed toward limiting the number of prescribed dosage units of opioid analgesics. Additionally, the mismatch between what was

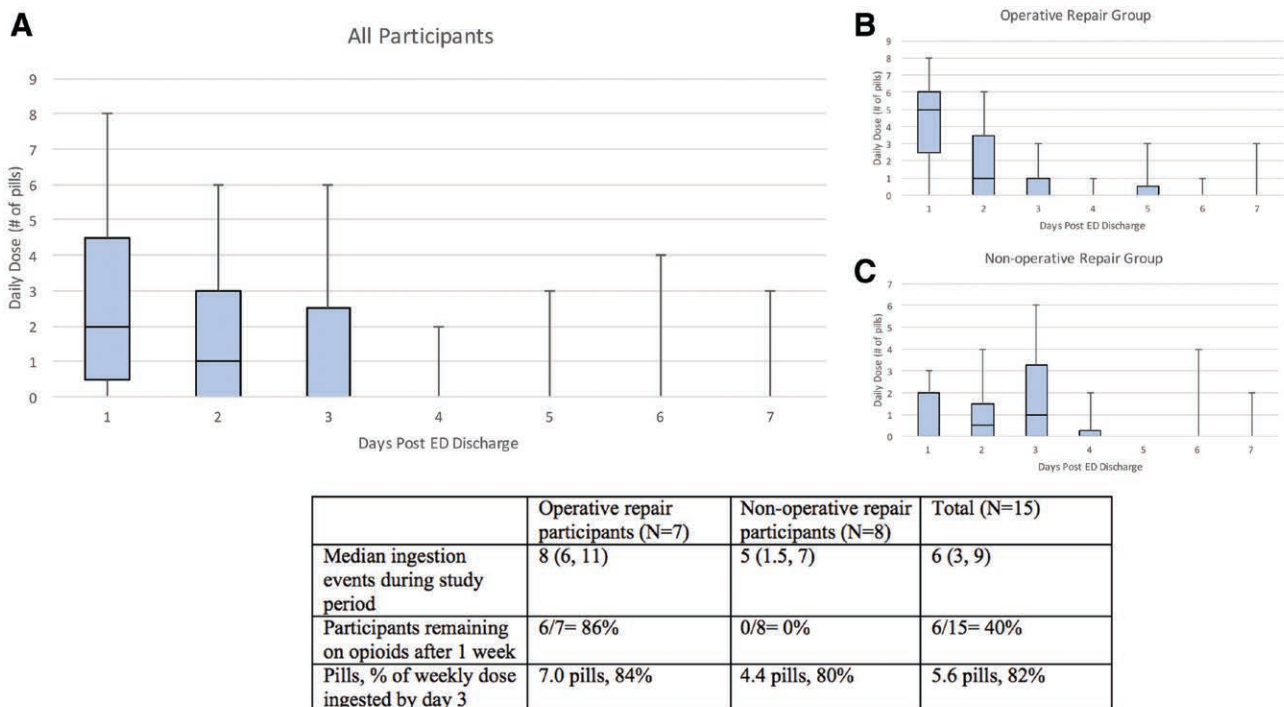


Figure 3. Median oxycodone ingestion events in all study participants (A), in participants who ultimately underwent operative repair (B), and in participants who ultimately underwent nonoperative repair (C). ED indicates emergency department.

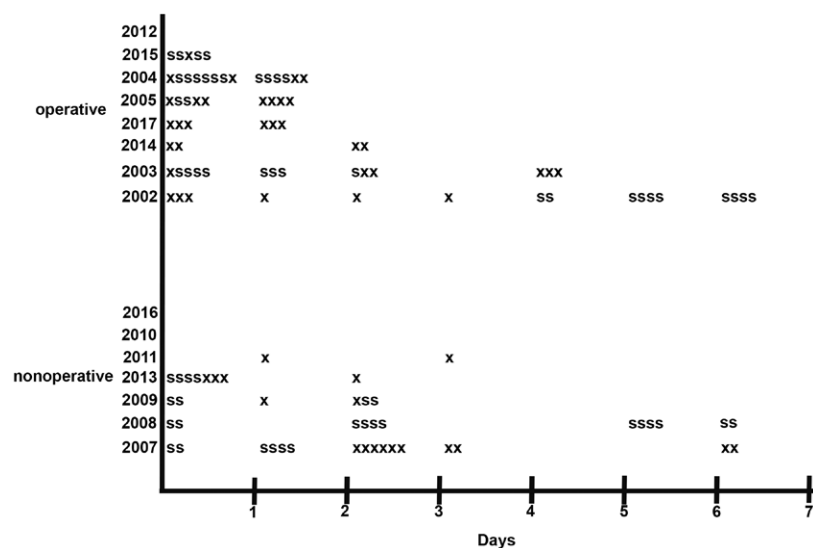


Figure 4. Ingestion events recorded by the oxycodone digital pill. “X” denotes recorded ingestion event, and “S” denotes recorded ingestion event that is part of a simultaneous (ingested 2 pills at 1 time) ingestion event recorded by the digital pill.

prescribed and what was self-administered underscores the importance of directed teaching to promote nonopioid analgesia (nonsteroidal antiinflammatory drugs and acetaminophen) among providers, despite it being potentially time consuming in a busy ED setting. Physicians should consider providing patients with anticipatory guidance regarding the expected duration of opioid use and the amount of opioids required. Understanding that patients likely need considerably fewer opioid dosage units that are commonly dispensed is important in preventing both downstream long-term opioid use and opioid diversion.²³ Our data regarding actual opioid utilization are consistent with other studies demonstrating that physicians significantly overprescribe opioids in response to acute pain.^{1,5,28}

Participants’ practice of ingesting opioid analgesics before sleep is concerning. Patients reported the concern of waking up at night with pain as the rationale for ingesting opioids before sleep, and indeed, this is a common informal instruction that patients receive from providers in recovery. This approach carries considerable risk, however, because of the respiratory depressant effect of opioids, which may exacerbate preexisting obstructive sleep apnea. Discharge instructions given to patients receiving opioid prescriptions should therefore include explicit warnings regarding the risk of new or worsening sleep apnea that may culminate in death.

Our ultimate goal is not to prevent physicians from prescribing opioids. Instead, our intent is to provide guidelines, based on direct observation, on how to best manage acute pain while preventing overdose and long-term misuse. Pain is not merely distressing; it is also therapeutic. Acute pain promotes healing by limiting an individual’s activity after injury. A careful balance must be struck between functional analgesia and opioid prescribing to avoid long-term nonmedical opioid use. Our data from digital pills that can detect patterns of opioid use are a novel and important step toward responsible and evidence-based opioid prescribing.

Limitations

This study has several limitations. First, it was conducted at a single academic tertiary ED. The demographics of

individuals presenting to our ED and their preferences for opioid analgesics may not be generalizable to other EDs in different settings. Second, the small number of participants enrolled in the study limits the ability to draw conclusions regarding the median number of opioid analgesics required to control acute pain. Despite this, our data suggest that individuals ingesting opioids for acute pain may use less opioids than previously thought. Future investigations will investigate opioid ingestion patterns after more homogeneous painful conditions (eg, acute pain after a specific surgical procedure). Third, this study focused on opioid-naïve individuals with acute fractures. Individuals with a history of opioid use may respond differently to acute exacerbations of pain producing different ingestion patterns. Fourth, we selected a single painful condition—acute fractures. Our results, while important, may be different in individuals with other painful conditions.

Implications for Further Research

With increasing restrictions on opioid prescribing, detecting opioid ingestion patterns in individuals provide greater precision in determining the numbers of opioid dosage units needed to treat pain while minimizing the threat of misuse. As an investigational tool, the digital pill provides not only a direct measure of opioid ingestion but also evidence of more dynamic changes in medication-taking behavior. Additionally, use of a digital pill technology, when linked to ecologic momentary assessments, can define affective and environmental contexts that surround opioid-taking behavior, such as whether opioid ingestion is linked to subjective notions of increasing pain or periods of stress.

We recognize that the technology associated with the digital pill described here may appear cumbersome and difficult to use. Despite this, we demonstrated that individuals, with short instruction in the ED, can operate digital pills in the real world. Iterative improvements in the technology will make digital pills more seamless; we project that there will be 2 major advances. First, we have witnessed, even during our study period, iterative improvement in energy harvesting in the digital pill. This is significant because improved energy harvesting allows the digital pill to transmit ingestion data

across a larger distance. Second, because of improved detection capabilities of the digital pill, the most cumbersome components of the digital pill (eg, the reader and associated patch) will miniaturize and integrate into other on-body technology like a smartwatch or the patient's smartphone. We believe that these advances will improve the overall acceptability of digital pills and allow expansion of this technology to observe opioid ingestion in disparate populations. The improved technology can also be used in future trials to observe differences in opioid use between different age groups, individuals with disparate risk factors and among various types of surgical procedures.

Clinically, the wireless delivery of opioid ingestion information allows interventions to be delivered to patients at the precise moment they are needed. The discovery of behaviors consistent with the development of tolerance—either an escalation of opioid dose or an increase in dosing frequency—can trigger interventions by clinicians in real time. The development of real-time interventions that are linked to specific patterns of opioid ingestion is an area of urgent need. ■■

DISCLOSURES

Name: Peter R. Chai, MD, MMS.

Contribution: This author helped in conceiving the study, recruiting the participants, completing the data analysis, and was principally responsible for the study as a whole and drafting the manuscript.

Name: Stephanie Carreiro, MD.

Contribution: This author helped in conceiving and completing the data analysis in this study and was also instrumental in providing key edits to the manuscript.

Name: Brendan J. Innes, BS.

Contribution: This author helped recruiting the participants, was primarily responsible for data analysis in the study, and providing key edits in the manuscript.

Name: Brittany Chapman, BS.

Contribution: This author helped in recruiting the participants, completing the data analysis, and providing key edits in the manuscript.

Name: Kristin L. Schreiber, MD, PhD.

Contribution: This author helped in drafting the manuscript and providing key edits in revisions of the manuscript and technical assistance in preparing figures and visualizing data for the manuscript.

Name: Robert R. Edwards, PhD.

Contribution: This author helped in drafting the manuscript and providing key edits in revisions of the manuscript.

Name: Adam W. Carrico, PhD.

Contribution: This author helped in drafting key portions of the manuscript and providing key edits in the revisions of the manuscript.

Name: Edward W. Boyer, MD, PhD.

Contribution: This author helped in conceiving the study, recruiting the participants, mentoring Peter R. Chai and Stephanie Carreiro in data analysis, drafting the manuscript, and providing the principle funding through 5K24DA037109 to acquire materials to perform the study.

This manuscript was handled by: Honorio T. Benzon, MD.

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