Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Electronic Real-Time Monitoring Reveals Limited Adherence to Long-Term Opioid Prescriptions in Pain Patients

David C Houghton[1,2], Christina R Merritt[1,3], Sierra N Miller[1], Jasmine M Mitchell[4], David Parker[1], Jonathan D Hommel[1,3], Kathryn A Cunningham[1–3,*], Denise M Wilkes[1,5,*]

[1]Center for Addiction Sciences and Therapeutics, University of Texas Medical Branch, Galveston, TX, USA; [2]Department of Psychiatry and Behavioral Sciences, University of Texas Medical Branch, Galveston, TX, USA; [3]Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, TX, USA; [4]Department of Family and Community Medicine, UT McGovern Medical School, Houston, TX, USA; [5]Department of Anesthesiology, University of Texas Medical Branch, Galveston, TX, USA

*These authors contributed equally to this work

Correspondence: David C Houghton, Center for Addiction Sciences and Therapeutics, University of Texas Medical Branch, 301 University Blvd, Texas, Galveston, TX 77555, USA, Tel +1 (409)747-9785, Email dahought@utmb.edu

Background: Pain management physicians are increasingly focused on limiting prescription opioid abuse, yet existing tools for monitoring adherence have limited accuracy. Medication event monitoring system (MEMS) is an emerging technology for tracking medication usage in real-time but has not been tested in chronic pain patients on long-term opioid regimens.

Objective: We conducted a pilot clinical trial to investigate the utility of MEMS for monitoring opioid adherence and compared to traditional methods including self-report diaries, urine drug screen (UDS), and physicians' opinions.

Methods: Opioid-maintained chronic pain patients were recruited from a pain management clinic. Participants (n=28) were randomly assigned to either receive MEMS bottles containing their opioid medication for a 90-day period or to continue using standard medication bottles. MEMS bottles were configured to record and timestamp all bottle openings and the number of pills that were removed from the bottle (via measurement of weight change).

Results: Participants who received MEMS demonstrated highly heterogenous dosing patterns, with a substantial number of patients rapidly removing excessive amounts of medication and/or "stockpiling" medication. By comparison, physicians rated all participants as either "totally compliant" or "mostly compliant". UDS results did not reveal any illicit drug use, but 25% of participants (n=7) tested negative for their prescribed opioid metabolite. MEMS data did not correlate with physician-rated adherence (P=0.24) and UDS results (P=0.77). MEMS data consistently revealed greater non-adherence than self-report data (P<0.001).

Conclusion: These results highlight the limits in our understanding of naturalistic patterns of daily opioid use in chronic pain patients as well as support the use of MEMS for detecting potential misuse as compared to routine adherence monitoring methods. Future research directions include the need to determine how MEMS could be used to improve patient outcomes, minimize harm, and aid in clinical decision-making.

Trial Registration: This study was preregistered on ClinicalTrials.gov (NCT03752411).

Keywords: medication event monitoring systems, chronic pain, medication adherence

Introduction

Background

Prescription opioids are effective for managing chronic pain, however opioid misuse and overdose pose significant threats to public health. Roughly 21–29% of prescription opioid-maintained patients (OMPs) engage in misuse[1] which can result in intoxication-related accidents (eg, car crashes, falls), development of opioid use disorder, overdose, and/or death. Moreover, with the enormous illicit demand for prescription opioids,[2] diversion of pharmaceutical-grade opioids

Received: 24 August 2023
Accepted: 15 April 2024
Published: 21 May 2024

has become a significant problem.[3–5] As a result, clinicians face increasing pressure to identify and prevent misuse and/or diversion among OMPs. This is an intimidating task, as identifying and addressing suspected misuse can have major ramifications for both patients and clinicians, such as denial of service and medicolegal liability, respectively. In this landscape, clinicians need adequate tools that help differentiate adherent from non-adherent prescription opioid usage. Unfortunately, evidence has shown that the adherence monitoring tools recommended by clinical practice guidelines (eg, self-report questionnaires, pill counts, urine drug screens [UDS] and prescription drug monitoring programs [PDMPs]) fail to accurately identify many cases of misuse.[6,7] Therefore, even when providers utilize the best available measures, many instances of non-adherence are likely undetected.

Existing prescription opioid adherence monitoring methods are limited by several key factors. Evidence shows that many patients conceal non-adherent behavior (eg, use of non-prescribed drugs)[8,9] and over-estimate their own medication adherence,[10,11] suggesting that self-reports of medication consumption may often contain inaccurate or falsified data. Adherence measures that do not rely on self-report are limited by their reliance on proxy measures of medication use behavior, which only provide vague insights into recent medication consumption.[12,13] For example, UDS results indicate whether the concentration of drug metabolite(s) is above a particular threshold, providing an indirect measure of whether a patient has recently consumed certain drugs. As such, UDS results are vulnerable to errors in interpretation, such as when non-detection of prescribed drug metabolites could indicate (a) finishing medication early, (b) infrequent use of the prescribed drug, and/or (c) diversion of prescribed drug. Such equivocal UDS findings appear to occur frequently as research has shown that, within a 12-month period in which OMPs underwent regular drug testing, up to 24% of patients exhibit at least one result indicating non-detection of prescribed drug.[14] These findings highlight the need for additional adherence monitoring strategies that provide more accurate and definitive data.

Prior Work

Technological solutions have been developed recently that enable real-time monitoring of medication usage. Studies have shown that medication event monitoring systems (MEMS), colloquially known as "smart bottles", can accurately detect when patients take doses and how many doses are taken.[15–17] Over 200 studies utilizing MEMS have been conducted for various medications and diseases,[15] yet a vast majority were conducted with medications that lack abuse potential. In the case of prescription opioids, MEMS data could conceivably detect previously unobservable behaviors such as excessive dosing, as well as tracking long-term patterns of usage that may indicate diversion (eg, removing all doses at once) or medication stockpiling (eg, absence of regular dosing and accumulation of doses over time). Few studies have examined the feasibility and acceptability of MEMS with prescription opioids,[18–26] and most were conducted on cancer pain with the goal of detecting underdosing, as opposed to excessive dosing.[18,21–25]

Three studies have been conducted to assess the feasibility of MEMS to detect opioid over-use in acute pain patients. One recent study, conducted in postpartum women after cesarean delivery who were discharged with short-term opioid regimens, examined the concordance between self-reported opioid usage and MEMS data, which was gathered via an electronic medication cap that recorded bottle openings.[26] Results of that study indicated that 67% of patients provided self-reports that corresponded closely to MEMS data, and only 16.67% of patients under-reported their opioid use (ie, a lesser amount of self-reported use than was documented by MEMS). Furthermore, two MEMS studies (n=10–15 participants) used a unique technology known as "digital pills" (eTectRx, Newbury, FL, USA) in short-term prescription opioid users. These capsules detect when doses are ingested using radiotracers (inserted into capsules) activated by digestive acids to emit signals to wearable receivers. The first study conducted in patients with a femur fracture who were discharged from the emergency department with a prescription opioid regimen identified only one patient who exceeded the total number of doses allotted for a single day. In this study, none of the patients ingested all 21 dispensed doses.[20] The second study, also conducted on patients discharged from the emergency department after bone fracture, observed four participants that exceeded daily maximum doses and only one participant that exceeded the daily maximum on more than one day.[19] The collective results of these studies suggest that MEMS are feasible for tracking prescription opioid use and that non-adherence rates in acute pain patients are not clinically significant. However, these findings may not generalize to long-term opioids prescribed for chronic pain.

Goal of Current Study

The current pilot study tested the efficacy of a non-invasive MEMS technology, the Nomi™ electronic pill bottle (SMRxT, Inc., New York, NY, USA) for monitoring prescription opioid adherence in patients diagnosed with chronic non-cancer pain. NOMI bottles are equipped with electronic caps and pressure sensors within the bottle which record bottle openings and weight changes, enabling tracking of when doses are removed and how many are removed. The bottles were filled with a monthly supply of the prescription opioid and dispensed on an as-needed prescription (*pro re nata*; PRN) for pain. Participants were masked to study procedures, thus reducing the propensity to change medication behavior to conform with expectations and monitored for three months. We first sought to examine MEMS data regarding individual, real-time patterns of opioid use behavior to gauge the qualitative potential for this technology to provide novel insights into the nature of PRN opioid use. Specifically, we were interested in the frequency with which participants' opioid use deviated significantly from expected patterns of use, such as excessive consumption of medication. Second, we sought to determine whether MEMS would provide discrepant adherence data as compared to routine adherence measures. UDS results and physicians' clinical judgments regarding participants' opioid adherence were compared to MEMS data. Based on the concept that MEMS data would provide more direct surveillance of opioid use behavior than the indirect measures (eg, self-report diaries) that typically inform clinical judgement, we hypothesized that UDS results and clinical judgment would not align with MEMS adherence data. Furthermore, in this randomized, parallel, single-blind clinical trial (50% allocation ratio to each condition), we examined whether the NOMI MEMS system would detect greater rates of non-adherent medication use behavior than self-report diaries of medication usage. Self-report diaries of medication usage are common in various medical settings[27] and consistent with standard of care. Because patients are presumably incentivized to portray themselves as highly adherent, we hypothesized that MEMS data would show greater rates of non-adherent behavior as compared to self-report diaries.

Materials and Methods

Recruitment

This study was preregistered on ClinicalTrials.gov (NCT03752411) and conducted from July 2019 to July 2020. The study was approved by the UTMB Institutional Review Board, complies with the Declaration of Helsinki, and followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines for social and psychological intervention trials. Patients were recruited from a pain management clinic at the University of Texas Medical Branch (UTMB). Inclusion criteria consisted of the following: (a) age between 18 and 75 years, (b) chronic pain duration ≥3 months, (c) primary diagnosis of musculoskeletal pain, (d) prescription for one opioid-containing analgesic medication, and (e) expectation that patient will return to clinic in three months. Exclusion criteria consisted of the following: (a) presence of pain due to cancer, chemotherapy or radiation treatment, or cancer-related surgery, (b) any surgery in last three months, (c) use of an intrathecal drug delivery device, (d) use of a spinal cord stimulator, (e) diagnosis of dementia, and (f) illiteracy. Potential participants were identified through screening of daily clinic rosters. Patients flagged as potentially eligible were asked by their physician if they would like to learn more about the study. If interested, research personnel introduced the study and conducted informed consent. After providing informed consent, participants were randomized to either the control condition (self-report diaries of medication usage) or the experimental condition (MEMS plus self-report diaries of medication usage). Therefore, all participants completed self-report diaries, but only participants assigned to the MEMS condition received a NOMI bottle. The participant's treating physician was aware of patients' participation in the study, but physicians were masked to condition assignment. Research personnel, except for the Principal Investigator (DMW), were aware of condition assignment due to the need to manage participants' receipt and return of NOMI bottles.

The study involved incomplete disclosure and deception, as participants were informed that the purpose of the study was to test a new prescription bottle that will monitor the physical environment inside the bottle. Study personnel described this bottle as measuring the temperature and humidity inside the bottle and around the medication. Participants were also asked to keep their medication in the bottles, to only remove doses immediately prior to ingestion, and to properly dispose of (or return) unused medication at the end of each month. It was further explained that participants

should not store their pain prescription in pill organizers, pockets/purses, or other containers. Participants were not informed that the bottles would record the number and timing of pills dispensed.

During study planning, the sample size was projected at n=96 based upon a power analysis indicating that n=43 per group would reach 70% power to detect a non-inferiority margin difference between group proportions of 20% based on a one-sided Z-test at 0.05 significance level, with 10% planned attrition rate (thus, planned over-recruitment of 10 participants). However, due to challenges associated with the COVID-19 pandemic (eg, fewer office visits, patient unwillingness to travel to return diaries or collect NOMI bottles from investigational drug pharmacy), participant recruitment and retention were less successful than anticipated. As shown in Figure 1, a total of n=96 participants were randomized with n=18 participants completing the MEMS arm of the study, and n=10 participants completed the control arm of the study.

Procedure

Participants randomly assigned to the MEMS condition received NOMI bottles containing their prescription medication, which were dispensed by the UTMB Investigational Drug Pharmacy. Participants in the control condition received their prescriptions from their normal, preferred pharmacy. In both groups, prescriptions were dispensed with 30-day dosages, thus requiring bottles to be filled three times across the 90-day study period, which is consistent with legal requirements in the United States. Those in the MEMS condition received a new NOMI bottle each month to preserve battery life. We offered to dispose of any unused medication, but no medication was returned during the study. All NOMI bottles were returned to study personnel, although 21 participants in the MEMS condition did not complete the study. All participants, regardless of the group assignment, received instructions to complete a daily pain medication diary in which they recorded the time and number of opioid doses taken. Medication diaries were collected at the end of the 90-day study by research personnel, and 38 participants who started the study failed to complete the protocol and did not return their diaries.

Data Collection

NOMI bottles were provided by SMRxT and assigned a unique bottle number to identify data collection to a specific unit. No further information or protected health information was shared with SMRxT. The pharmacists, assigned to this study, associated bottle numbers to specific participants, which were all allocated unique study identification numbers. This information was shared with SMRxT and made available to the research team after completion of data collection. NOMI

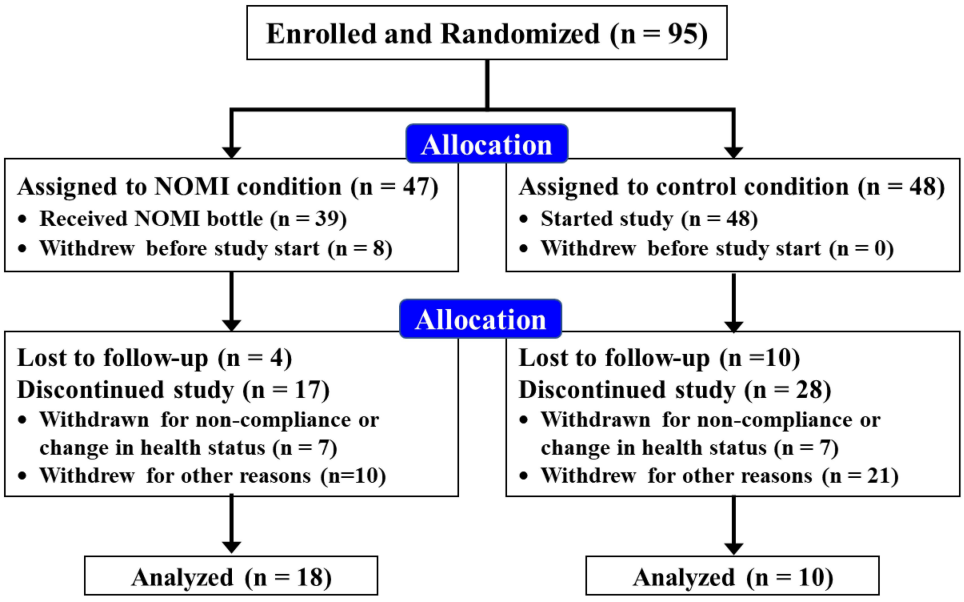

Figure 1 The CONSORT Flow Diagram for the NOMI Randomized, Parallel, Single-Blind Clinical Trial.

bottles were configured to record weight changes in the bottles and time stamp these weight changes. Data were transmitted in real time over the Verizon cellular network to SMRxT. Weight changes were then converted to represent number of doses removed based on the weight of individual pills, which were weighed by the Investigational Drug Pharmacy for each type of medication prescribed to participants. Individual daily pain medication diaries were distributed to patients in the form of paper surveys, in which participants were instructed to record each instance of medication use by the time and date of ingestion. Further, during recruitment, the referring pain management physician was asked to provide a rating of their perception, or clinical judgment, regarding the adherence/compliance of the participant on a 4-point ordinal scale corresponding to 0 ("Questionable Compliance"), 1 ("Somewhat Compliant"), 2 ("Mostly Compliant"), or 3 ("Compliant"). Additional data were collected via retrospective chart reviews. Data collected from the electronic health records included age, gender, pain diagnoses, medication characteristics (eg, name and dose), and the most recent UDS result. UDS were conducted via immunoassay, which consisted of testing for the metabolites of the prescribed drug as well as those of illicit drugs. Positive UDS results indicating illicit drug use (or non-detection of prescribed drug) were confirmed via liquid chromatography-mass spectrometry.

Ethical Considerations

The study was reviewed and approved by the UTMB Institutional Review Board. Informed consent was obtained from all participants prior to enrollment. All data reported herein have been deidentified and are subject to standard human subjects' confidentiality protections.

Although participants were misled regarding the MEMS device during the informed consent process and throughout data collection, the purpose of the study was disclosed to participants at the 3-month follow-up visit in the pain management clinic. Debriefing occurred in an office adjacent to the clinic to ensure privacy and maintain participant masking. Participants were asked at debriefing to provide final permission to use their data collected during the study, with the option to withdraw their participation and have their study data destroyed. No participants opted to withdraw during debriefing. Data remained masked to treating physicians and were analyzed by the research team after completion of all data collection. Participants received a $5 Walmart gift card for each returned NOMI bottle or each returned diary and $10 to complete end-of-study questionnaires for a total compensation of $25.

Statistical Analyses

Analyses were performed using R Statistical Software (v4.1.0). To determine the quality of random assignment in the trial, baseline characteristics of participants assigned to each condition were compared using Mann–Whitney *U*-tests and chi-square tests of independence. Spearman correlations were used to determine whether physicians' perceptions of participant adherence predicted scores from MEMS or self-report diaries. Comparisons between outcome measures (UDS results, physician-rated adherence, MEMS scores, and diary data) were conducted using Mann–Whitney *U*-tests. Comparisons of medication adherence rates between study condition and adherence monitoring method (MEMS versus self-report diary) were also conducted using Mann–Whitney *U*-tests.

There is no established method for summarizing or analyzing data from MEMS,[15,28] particularly for drugs with abuse potential. In the current study, we were interested in identifying both over- and under-use of medication, but because we know so little about chronic pain patients PRN opioid usage, we first inspected individual patterns of medication use across each month of the study period. Patients on long-term PRN opioids were dispensed a 30-day supply of medication with instructions to take up to the recommended (ie, maximum) dose per day as needed to control pain. Participants in the current study were on stable regimens of prescription opioids, meaning their dosing schedule should adequately control pain and a 30-day supply of medication should not be exhausted long before the next refill. Likewise, participants should use their medication regularly based on their stated need for analgesia, meaning that patients who need less medication than prescribed should communicate this to their provider and decrease their prescribed monthly supply. Significant accumulation of doses, or stockpiling, should therefore not occur. We compiled MEMS data regarding the number and timing of doses to reflect the percentage of total monthly supply remaining in the bottle over the course of each month. Although there are no quantitative benchmarks for identifying over- or under-use according to this method, we surmised that adherent medication usage should be reflected by a steady linear decrease in monthly supply over the

course of 30 days. In contrast, rapid removal of medication should be reflected by a steep drop in total supply and stockpiling should be reflected by a flat (or increasing) total supply.

Additional quantitative analysis of medication usage was conducted according to a novel strategy. While most MEMS studies have summarized data by computing the proportion of adherent dosing periods within all dosing periods across the monitoring period, this strategy could be seen as insufficient in accounting for both over- and under-use, as days in which too many doses are removed would be coded the same as days in which no doses are removed when in fact there are qualitative differences between these behaviors. We thus formulated a coding method that differentially categorized "non-adherent" dosing periods in which too many doses were taken from those in which no doses were taken. As such, days in which no medication was removed from the bottle were coded as "0", whereas days in which participants removed excessive doses were coded as "-1". Instances in which participants added medication to the bottle were also penalized with a score of "-1". Adherent days (at least one dose removed but no more than maximum) were coded as "1". Daily scores were averaged over the course of each 30-day prescription refill period and over the 90-day total study observation period.

Results

Participant Characteristics and Retention

There were no baseline differences between participants randomized to either the MEMS or control condition based on gender [$X^2(1, N=95)=0.03$, $P=0.87$], age [$t(26)=0.67$, $P=0.50$] or morphine equivalent daily dose (MEDD) ($P=0.85$). However, the randomized cohorts did differ in medication type [$X^2(1, N=95)=11.85$, $P=0.003$]. There were no differences between participants groups for physician-rated adherence or UDS results (all P-values≥.13). In participants assigned to the MEMS condition, there were no differences between persons who completed or did not complete the study (all P-values≥0.37). In participants randomized to the control condition, there were no differences between those who completed versus did not complete the study in age, gender, or MEDD (all P-values≥.54), but there were differences in medication type [$X^2(1, N=48)=6.43$, $P=0.040$].

Detailed descriptions of study completers are provided in Table 1. There were no differences between experimental conditions among study completers regarding gender, age, or MEDD (all P-values≥.65), but there were differences in the type of medication prescribed [$X^2(1, 29)=13.88$, $P=0.001$].

Table 1 Participant Characteristics

ID#*	Condition	Gender	Age	MedicationType	Dose (mg)	Daily Dosing	MME
1	MEMS	F	59	Tramadol	50	BID	10
2	Control	F	69	Hydrocodone	10	QD	10
3	MEMS	F	68	Hydrocodone	10	BID	20
4	Control	M	55	Hydrocodone	10	BID	20
5	MEMS	F	50	Tramadol	50	QD	5
6	MEMS	F	70	Hydrocodone	5	BID	10
7	MEMS	M	57	Tramadol	50	BID	10
8	MEMS	F	58	Codeine	30	BID	9
9	Control	F	68	Codeine	30	BID	9
10	Control	F	73	Codeine	30	BID	9
11	MEMS	F	73	Tramadol	50	QD	5

(*Continued*)

Table 1 (Continued).

ID#*	Condition	Gender	Age	MedicationType	Dose (mg)	Daily Dosing	MME
12	MEMS	M	66	Tramadol	50	BID	10
13	Control	F	63	Hydrocodone	5	BID	10
14	MEMS	M	70	Hydrocodone	10	QD	10
15	MEMS	F	58	Hydrocodone	10	BID	20
16	MEMS	F	62	Tramadol	50	TID	15
17	MEMS	M	71	Tramadol	50	TID	15
18	Control	F	66	Hydrocodone	10	BID	20
19	MEMS	F	41	Tramadol	50	TID	15
20	Control	F	36	Hydrocodone	10	BID	20
21	MEMS	F	65	Hydrocodone	10	BID[δ]	16.7
22	MEMS	M	51	Tramadol	50	BID	10
23	MEMS	F	53	Tramadol	50	TID	15
24	MEMS	M	63	Tramadol	50	BID	10
25	MEMS	F	50	Tramadol	50	BID	10
26	Control	F	65	Hydrocodone	7.5	QD	7.5
27	Control	F	47	Codeine	30	BID	9
28	Control	M	65	Codeine	30	BID	9

Notes: MME conversions for prescription opioids derived from CDC guidelines[7]. [δ]Participant was prescribed 50 doses for one month, thus dosing should be BID most days and QD some days. *Participant numbers reported herein were generated post-hoc to bolster confidentiality.

Abbreviations: QD, Once daily; BID, Twice daily; TID, Three times daily; MME, morphine milligram equivalents.

Medication Adherence

Visual inspection of MEMS data revealed heterogeneous medication usage patterns. As shown in Figure 2, the supply of medication was steadily depleted amongst many participants, thus reflecting consistent and appropriate dosing (expected pattern of use shown in black line with triangular data points). However, several sharp decreases in medication supply over short time periods were observed, and a substantial portion of participants ran out of medication before 30 days had elapsed. These data could reflect over-consumption or diversion of medication. There were additional notable instances in which participants added medication to the bottle, which may reflect stockpiling of medication. Finally, data from several participants showed lengthy time periods in which no medication was consumed, thus indicating decreased need for analgesia than is being reported to their physician. Several participants indeed appeared to have consumed no medication for most of the month and removed the entirety of their supply on a single day. Notably, the addition of excess medication into NOMI bottles appears to have increased over the course of the study, as evidenced most clearly by one participant accumulating nearly 3x the expected weight during Month 3. Data from Months 2 and 3 (Figures 3 and 4) largely demonstrated the same patterns, in that some participants consistently removed small numbers of doses while others quickly ran through their supply, removed less medication than expected, or accumulated medication within the bottles. Spearman correlations of MEMS scores between months 1–3 indeed showed that patterns of medication usage were largely consistent (all P-values$\leq$.001).

Physician-reported adherence for each participant is provided in Table 2, along with adherence scores based on MEMS data and self-report diaries. Overall, physician reports conveyed strong confidence that patients were either

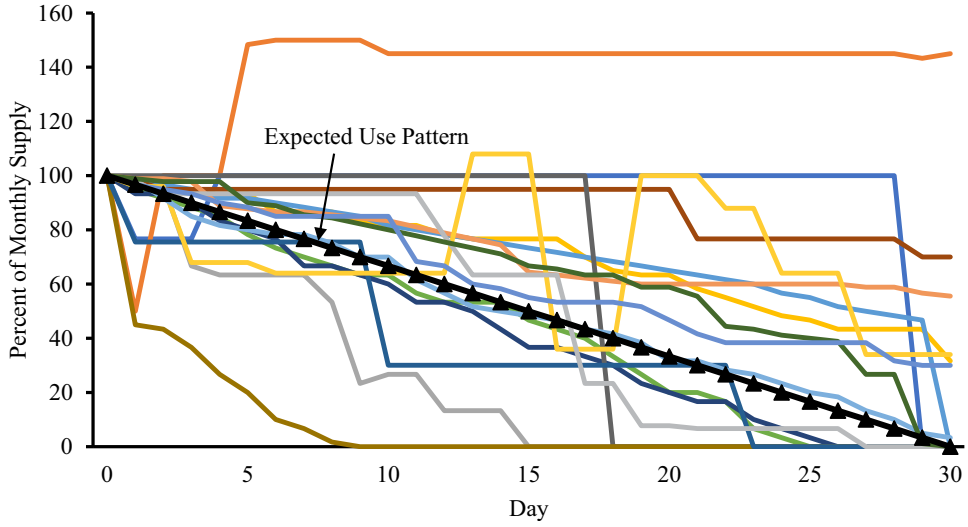

Figure 2 NOMI Tracking of Medication Supply over Month 1.
Note: Data from one participant are unavailable due to a mechanical error.

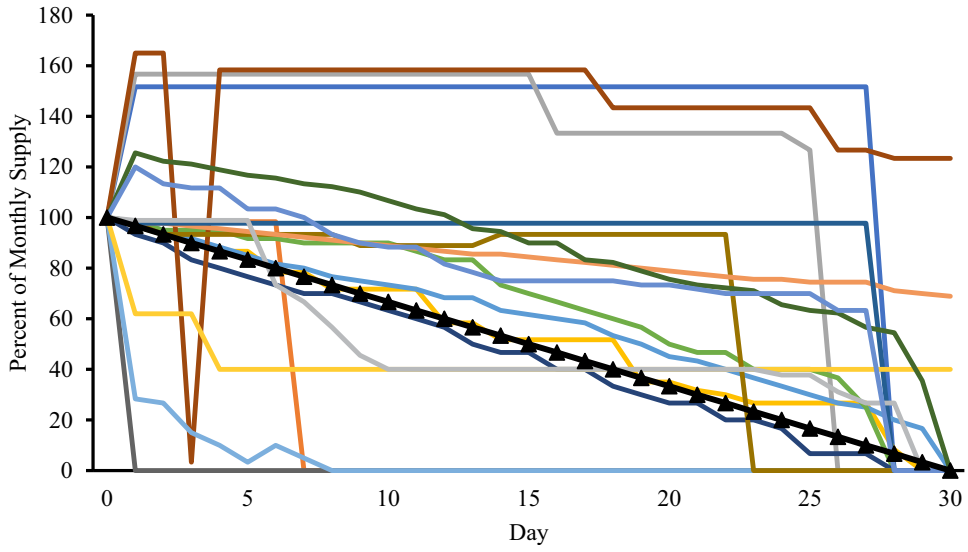

Figure 3 NOMI Tracking of Medication Supply over Month 2.
Note: Data from one participant are unavailable due to a mechanical error.

totally compliant or mostly compliant. UDS results showed that no participant tested positive for an illicit substance or other prescription drug (eg, unauthorized benzodiazepine), therefore test results consisted of positive or negative detection of the prescribed opioid metabolite. Consistent with our predictions, physicians' perceptions of patient adherence did not align with other adherence monitoring measures, as evidenced by non-significant associations with UDS results (W=74, P=0.77), MEMS scores (ρ=−0.03, P=0.89), and self-report diary scores within either condition (ρ=0.261, P=0.32; ρ=−0.293, P=0.41). UDS results were also not associated with adherence as measured by MEMS scores (W=23, P=0.24) or self-reported diaries within either condition (W=21, P=0.37; W=0, P=0.17). Our hypothesis that MEMS data would reveal greater non-adherence than self-report data was supported, as scores from MEMS (Md = −0.03, IQR=−0.08, 0.14) were significantly lower than scores from diaries from participants in the MEMS condition (Md =0.75, IQR=0.30, 0.93; W=26.5, P<0.001) as well as from participants in the control condition (Md =0.94, IQR=0.69, 1.0; W=11.5, P<0.001). There was no significant difference between the diary scores of participants in the MEMS condition and participants in the control condition (W=58, P=0.18).

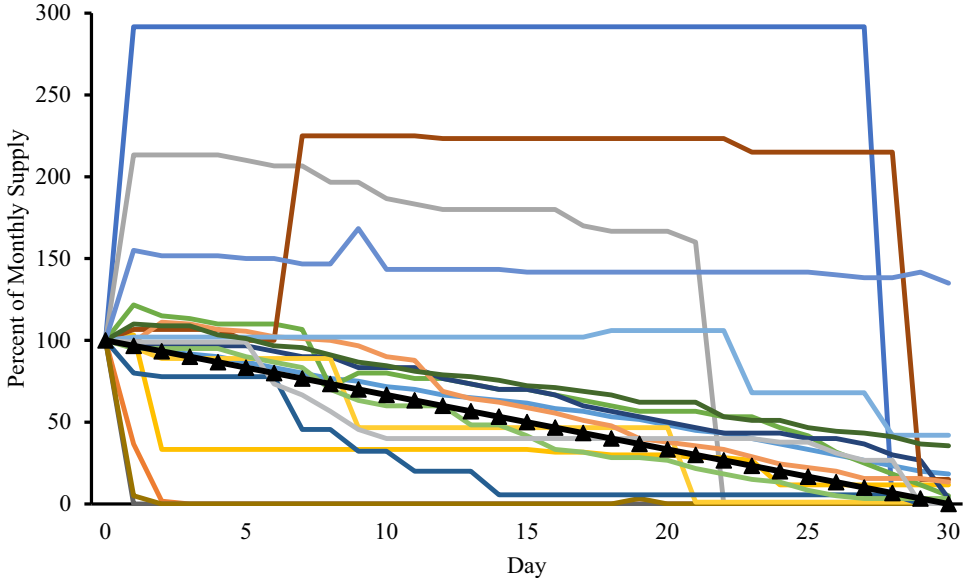

Figure 4 NOMI Tracking of Medication Supply over Month 3.

Discussion

Principle Results

The current study examined the feasibility of MEMS technology, NOMI "smart" bottles, to capture real-time patterns of long-term prescription opioid use in chronic pain patients. Real-time MEMS data showed heterogeneous opioid use patterns that frequently suggested non-adherent behavior. In addition, we examined whether MEMS data would reveal

Table 2 Adherence Scores

Participant	Condition	Physician Ratings	MEMS 90-day Adherence	Diary 90-day Adherence
1	MEMS	Compliant	−0.078	†
3	MEMS	Mostly Compliant	−0.056	0.977
5	MEMS	Compliant	−0.067	0.285
6	MEMS	Compliant	0.100	0.932
7	MEMS	Compliant	0.833	0.944
8	MEMS	Compliant	0.144	0.125
11	MEMS	Compliant	0.211	0.926
12	MEMS	Compliant	−0.078	0.274
14	MEMS	Compliant	−0.033	0.731
15	MEMS	Compliant	−0.250	0.304
16	MEMS	Compliant	−0.017	0.930
17	MEMS	Compliant	0.589	1.0
19	MEMS	Compliant	−0.089	0.749

(*Continued*)

Table 2 (Continued).

Participant	Condition	Physician Ratings	MEMS 90-day Adherence	Diary 90-day Adherence
21	MEMS	Mostly Compliant	−0.167	0.833
22	MEMS	Mostly Compliant	0.111	0.370
23	MEMS	Mostly Compliant	−0.189	0.103
24	MEMS	Compliant	0.367	0.979
25	MEMS	Compliant	0.122	0.662
2	Control	Compliant	-	0.393
4	Control	Compliant	-	1.0
9	Control	Compliant	-	0.667
10	Control	Compliant	-	0.967
13	Control	Compliant	-	1.0
18	Control	Mostly Compliant	-	0.922
20	Control	Mostly Compliant	-	1.0
26	Control	Mostly Compliant	-	0.766
27	Control	Mostly Compliant	-	0.100
28	Control	Mostly Compliant	-	1.0

Note: †Missing data.

greater rates of non-adherence as compared to traditional adherence monitoring methods. MEMS data indeed contained greater rates of non-adherence as compared to the self-report diaries, and we observed a lack of correlation between MEMS data, physician-rated adherence, and UDS results.

A general assumption is that, when opioids are prescribed appropriately, the rate of misuse will be minimal,[29] but this issue remains controversial.[30,31] Our present findings among pain management physicians, who adhere to opioid prescribing guidelines outlined by the Centers for Disease Control and utilize multiple forms of adherence monitoring (eg, PDMPs, UDSs), reflect the notion that clinicians believe their patients are largely adherent. However, the dosing patterns illustrated by our data suggest that non-adherent behavior may be common in OMPs and that opioid prescribers may frequently over-estimate adherence. While there are potentially benign explanations for the abnormal patterns of medication use (discussed below), we clearly observed that OMPs often use their medication in unexpected ways. Likewise, our results suggest that self-report records of opioid usage provide an over-estimation of adherence and that real-world use of PRN opioids differs from what patients admit. As such, our results could be seen to suggest that we know less about PRN long-term opioid use than previously believed, and that more studies utilizing real-time observation methods are clearly needed.

A particularly surprising insight gleaned from MEMS data was the frequent addition of excess medication into the bottles. While it is possible that some instances of this behavior may have benign explanations (discussed below), the data could be seen as substantiating findings related to the growing problem of prescription opioid stockpiling. A meta-analysis of studies examining adherence with prescription opioid medication indeed found that the rate of under-use is greater than the rate of over-use (29.9% vs 13.7%).[12] Furthermore, a study by the National Community Pharmacists Association reported that 40% of prescribed drugs are unused,[32] and a survey of 152 OMPs found that 63% planned to keep unused prescription opioids.[33] Patients in the latter study who reported plans to keep unused opioids cited several explanations such as (a) intentions to use the medication for a future pain, (b) ability to give to a family member or friend

for pain, and (c) a belief that prescription opioids have inherent value and that it would be wasteful to dispose of them. Despite these somewhat benevolent intentions, unused prescription opioids are dangerous and often make their way into the wrong hands, as research has shown that approximately half of persons who illegally use prescription opioids obtained the drug from friends or family.[34] Our current results showcase the ease with which OMPs can accumulate a large volume of medication and demonstrate how such behavior would likely go unnoticed by alternative adherence monitoring methods, thus supporting MEMS as a potentially useful tool for identifying stockpiling.

Additional research is needed to determine how physicians can effectively utilize MEMS data to improve adherence and outcomes in OMPs. For example, prescription opioid misuse has been defined as use that is contrary to the directed or prescribed pattern of use, regardless of the presence or absence of harm.[1] According to this definition, all our participants misused opioids on at least one occasion. This definition of misuse may be too broad and incompatible with PRN dosing, in which some degree of variation from the prescribed pattern of use is typically allowed based on varying individual patient needs. Therefore, MEMS data on prescription opioid use require interpretation within the context of additional sources of information, such as fluctuations in pain severity, current life events, and the patient's history. Clinicians who observe anomalous dosing patterns in real-time MEMS data could respond in several ways, such as querying the patient for an explanation, sending a reminder of dosing guidelines, scheduling a UDS, or warning the patient that their current dosing is inappropriate and must be corrected. Moreover, clinicians would benefit from additional research that examines the efficacy of such MEMS-based adherence interventions which could form the foundation of employing this emerging technology for best clinical practices.

Limitations

Even as our results provoke new insights, the NOMI MEMS system has several limitations. It is impossible to conclusively determine that aberrant behavior, as recorded by the MEMS system, reflects misuse or diversion. Patients in our study were instructed only to remove doses immediately prior to ingestion, but patients could presumably have forgotten or ignored these instructions and transferred their medication to other forms of storage. Likewise, the weight increases in the bottle detected by MEMs could reflect the addition of any similar weight medication, based perhaps on benign intentions. Another possible limitation relates to the dispensation of NOMI bottles through an investigational drug pharmacy, which could have biased data from participants in the MEMS cohort. Solving these problems and developing effective means for implementing and interpreting MEMS data are therefore a worthy subject of future investigations.

There are additional limitations to the current study, the most notable of which involved recruitment and retention of participants, which occurred due to challenges imposed during the COVID-19 pandemic. While we found that the characteristics of participants who completed the study did not significantly differ from non-completers, we cannot rule out the possibility that the results may differ under conditions of improved retention. Likewise, the small sample sizes preclude generalization of findings to the population of long-term OMPs and results could significantly differ in larger groups. Modeling opioid use behavior would have also been aided by the inclusion of data regarding daily pain symptoms, functionality, mood, and treatment satisfaction.

Conclusions

The results of the present study contain hypothetically significant clinical implications for long-term prescription opioid adherence, even under consideration of caveats, and serve to further emphasize the need for continued research and novel tools to assist providers in caring for their patients while also mitigating the misuse and diversion of prescription opioids.

Abbreviations

CONSORT, Consolidated Standards of Reporting Trials; MEDD, morphine equivalent daily dose; MEMS, medication event monitoring systems; OMP, opioid-maintained patients; PDMP, prescription drug monitoring program; PRN, *pro re nata*.

Data Sharing Statement

The data sets generated during and/or analyzed during the current study are available from Dr Denise Wilkes (dwilkes@utmb.edu) upon reasonable request.

Acknowledgments

This study was supported by pilot funding from the UTMB Center for Addiction Research, a grant (KAC, DMW) from the UTMB Clinical and Translational Award (CTSA; UL1TR001439), a grant (DCH, DMW, KAC) from NINDS (RM1NS128787), an Institutional Career Development Award Core Grant (DCH; 5KL2TR001441) and Predoctoral Fellowships (CRM; T32DA007287), (SNM; TL1TR001440). We also thank SMRxT Inc. for providing NOMI systems at reduced cost and for their technical support. SMRxT supported data collection via their electronic network but was not involved in the study design, data analysis, and interpretation, or in reviewing and approving the manuscript for publication.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed to the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

JMM is now with the Department of Family Medicine, Memorial Hermann Medical Group Clear Lake, Houston, TXDP is now with Christus Health Stanta Rosa Hospital in San Antonio, TXSNM is now with the Department of Neurobiology, University of Alabama at Birmingham, Birmingham AL. KAC is a consultant for Delix Therapeutics, unrelated to the present work. The authors report no other conflicts of interest in this work.

References

1. Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. *Pain*. 2015;156(4):569–576. doi:10.1097/01.j.pain.0000460357.01998.f1
2. Davis WR, Johnson BD. Prescription opioid use, misuse, and diversion among street drug users in New York City. *Drug Alcohol Depend*. 2008;92(1–3):267. doi:10.1016/j.drugalcdep.2007.08.008
3. Launonen E, Alho H, Kotovirta E, Wallace I, Simojoki K. Diversion of opioid maintenance treatment medications and predictors for diversion among Finnish maintenance treatment patients. *Int J Drug Policy*. 2015;26(9):875–882. doi:10.1016/j.drugpo.2015.03.007
4. McCabe SE, Cranford JA, Boyd CJ, Teter CJ. Motives, diversion and routes of administration associated with nonmedical use of prescription opioids. *Addict Behav*. 2007;32(3):562–575. doi:10.1016/j.addbeh.2006.05.022
5. Winstock AR, Lea T, Sheridan J. Prevalence of diversion and injection of methadone and buprenorphine among clients receiving opioid treatment at community pharmacies in New South Wales, Australia. *Int J Drug Policy*. 2008;19(6):450–458. doi:10.1016/j.drugpo.2007.03.002
6. Klimas J, Gorfinkel L, Fairbairn N, et al. Strategies to identify patient risks of prescription opioid addiction when initiating opioids for pain: a systematic review. *JAMA Network Open*. 2019;2(5):e193365. doi:10.1001/jamanetworkopen.2019.3365
7. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain--United States, 2016. *JAMA*. 2016;315(15):1624–1645. doi:10.1001/jama.2016.1464
8. Berndt S, Maier C, Schutz HW. Polymedication and medication compliance in patients with chronic non-malignant pain. *Pain*. 1993;52(3):331–339. doi:10.1016/0304-3959(93)90167-N
9. Timmerman L, Stronks DL, Groeneweg JG, Huygen FJ. Prevalence and determinants of medication non-adherence in chronic pain patients: a systematic review. *Acta Anaesthesiol Scand Apr*. 2016;60(4):416–431. doi:10.1111/aas.12697
10. Osterberg L, Blaschke T. Adherence to medication. *New Engl J Med*. 2005;353(5):487–497. doi:10.1056/NEJMra050100
11. Stirratt MJ, Dunbar-Jacob J, Crane HM, et al. Self-report measures of medication adherence behavior: recommendations on optimal use. *Transl Behav Med*. 2015;5(4):470–482. doi:10.1007/s13142-015-0315-2
12. Broekmans S, Dobbels F, Milisen K, Morlion B, Vanderschueren S. Medication adherence in patients with chronic non-malignant pain: is there a problem? *Eur J Pain*. 2009;13(2):115–123. doi:10.1016/j.ejpain.2008.02.010
13. Stewart SF, Moon Z, Horne R. Medication nonadherence: health impact, prevalence, correlates and interventions. *Psychol Health*. 2022;1–40. doi:10.1080/08870446.2022.2144923
14. Larochelle MR, Cruz R, Kosakowski S, et al. Do urine drug tests reveal substance misuse among patients prescribed opioids for chronic Pain? *J Gen Intern Med*. 2021;37:2365–2372. doi:10.1007/s11606-021-07095-8
15. Hartman L, Lems WF, Boers M. Outcome measures for adherence data from a medication event monitoring system: a literature review. *J Clin Pharm Ther*. 2019;44(1):1–5. doi:10.1111/jcpt.12757

16. Russell CL, Ashbaugh C, Peace L, et al. Time-in-a-bottle (TIAB): a longitudinal, correlational study of patterns, potential predictors, and outcomes of immunosuppressive medication adherence in adult kidney transplant recipients. *Clin Transplant Sep-Oct*. 2013;27(5):E580–90. doi:10.1111/ctr.12203
17. Faisal S, Ivo J, Lee C, Carter C, Patel T. The usability, acceptability, and functionality of smart oral multidose dispensing systems for medication adherence: A scoping review. *J Pharm Pract*. 2020;897190020977756. doi:10.1177/0897190020977756
18. Meghani SH, Knafl GJ. Patterns of analgesic adherence predict health care utilization among outpatients with cancer pain. *Patient Prefer Adherence*. 2016;10:81–98. doi:10.2147/PPA.S93726
19. Chai PR, Carreiro S, Innes BJ, et al. Oxycodone ingestion patterns in acute fracture pain with digital pills. *Anesth Analg*. 2017;125(6):2105–2112. doi:10.1213/ANE.0000000000002574
20. Chai PR, Carreiro S, Innes BJ, et al. Digital pills to measure opioid ingestion patterns in emergency department patients with acute fracture pain: A pilot study. *J Med Internet Res*. 2017;19(1):e19. doi:10.2196/jmir.7050
21. Oldenmenger WH, Echteld MA, de Wit R, et al. Analgesic adherence measurement in cancer patients: comparison between electronic monitoring and diary. *J Pain Symptom Manage*. 2007;34(6):639–647. doi:10.1016/j.jpainsymman.2007.01.015
22. Oldenmenger WH, Sillevis Smitt PAE, de Raaf PJ, van der Rijt CCD. Adherence to analgesics in oncology outpatients: Focus on taking analgesics on time. *Pain Pract*. 2017;17(5):616–624. doi:10.1111/papr.12490
23. Yeager KA, Williams B, Bai J, et al. Factors related to adherence to opioids in black patients with cancer pain. *J Pain Symptom Manage*. 2019;57(1):28–36. doi:10.1016/j.jpainsymman.2018.10.491
24. Finan PH, Carroll CP, Moscou-Jackson G, et al. Daily opioid use fluctuates as a function of pain, catastrophizing, and affect in patients with sickle cell disease: An electronic daily diary analysis. *J Pain*. 2018;19(1):46–56. doi:10.1016/j.jpain.2017.08.010
25. Wright EM, El-Jawahri A, Temel JS, et al. Patient patterns and perspectives on using opioid regimens for chronic cancer pain. *J Pain Symptom Manage*. 2019;57(6):1062–1070. doi:10.1016/j.jpainsymman.2019.02.023
26. Schirle LM, Dietrich MS, Lam L, Stone AL, Bruehl S, Osmundson SS. Accuracy of patient-reported versus real-time electronic postoperative opioid use outcomes. *American Journal of Obstetrics & Gynecology MFM*. 2021;3(4):100347. doi:10.1016/j.ajogmf.2021.100347
27. Lehmann A, Aslani P, Ahmed R, et al. Assessing medication adherence: options to consider. *Int J Clin Pharm*. 2014;36(1):55–69. doi:10.1007/s11096-013-9865-x
28. Kelly A, Crimston-Smith L, Tong A, et al. Scope of outcomes in trials and observational studies of interventions targeting medication adherence in rheumatic conditions: A systematic review. *J Rheumatol*. 2020;47(10):1565–1574. doi:10.3899/jrheum.190726
29. Schatman ME, Vasciannie A, Kulich RJ. Opioid moderatism and the imperative of rapprochement in pain medicine. *J Pain Res*. 2019;12:649–657. doi:10.2147/JPR.S198849
30. Rose ME. Are Prescription opioids driving the opioid crisis? assumptions vs facts. *Pain Med*. 2018;19(4):793–807. doi:10.1093/pm/pnx048
31. Lajam CM, Cenname J, Hutzler LH, Bosco JA. Ethics of opioid prescriber regulations: physicians, patients, and pain. *J Bone Joint Surg Am*. 2019;101(23):e128. doi:10.2106/JBJS.19.00437
32. Lewis ET, Cucciare MA, Trafton JA. What do patients do with unused opioid medications? *Clin J Pain*. 2014;30(8):654–662. doi:10.1097/01.ajp.0000435447.96642.f4
33. Buffington DE, Lozicki A, Alfieri T, Bond TC. Understanding factors that contribute to the disposal of unused opioid medication. *J Pain Res*. 2019;12:725–732. doi:10.2147/JPR.S171742
34. Substance Abuse and Mental Health Services Administration. Key substance use and mental health indicators in the United States: Results from the 2016 National Survey on Drug Use and Health (HHS Publication No. SMA 17-5044, NSDUH Series H-52); available from: https://www.samhsa.gov/data/sites/default/files/NSDUH-FFR1-2016/NSDUH-FFR1-2016.htm. Accessed April 30, 2024.