Original Article

Inpatient Prescribing and Monitoring of Fentanyl Transdermal Systems: Adherence to Safety Regulations

Theresa McEvoy, PharmD, BCPS^{*}; Joann Moore, RPh[†]; and Joyce Generali, RPh, MS, FASHP[‡]

ABSTRACT

Background: National safety guidelines were developed to minimize the occurrence of serious adverse drug events (ADEs) associated with the use of the fentanyl transdermal system (FTS), however, reports of use in opioid-naïve patients for treatment of acute pain and associated ADEs continue to occur.

Objective: To evaluate the prescribing patterns of the FTS for adherence to recent US regulatory recommendations and identify the impact of health information technology (HIT) on adherence rates.

Methods: A retrospective pre- and postintervention analysis was performed in hospitalized adult patients receiving FTS. Electronic medication order instructions and text questions were incorporated into FTS electronic medication orders. The primary outcome measure was adherence of FTS medication orders to regulatory guidelines defined as (a) a new order in an opioid-tolerant patient for use in moderate to severe chronic pain or (b) continuation of the documented home dose in use for at least 7 days. Safety measures included respiratory rate and documented ADEs.

Results: Adherence rates were significantly increased in the postintervention cohort as compared to the preintervention cohort (48.7% vs 85.0%; $P < .0001$). Incidence of ADEs was significantly lower post intervention (34.7% vs 23.3%; $P = .043$), including a lower incidence of respiratory depression (16.7% vs 8.3%; $P = .043$). Documentation was increased in the postintervention cohort (76% vs 100%). However, supporting documentation confirmed responses in only 59.2% of records reviewed.

Conclusions: Incorporation of HIT via electronic order text questions increased overall adherence rates to regulatory recommendations, increased documentation, and decreased the rate of associated ADEs.

Key Words—adverse drug event, fentanyl transdermal, health care informatics, medication safety

Hosp Pharm 2014;49:942–949

The fentanyl transdermal system (FTS) is designed to deliver a continuous dose of fentanyl, a potent opioid analgesic. Adverse events related to toxicity include sedation and respiratory depression, particularly in the opioid-naïve patient and when the FTS is abused or misused. To minimize the risk of severe and potentially fatal adverse drug events (ADEs), national warnings and guidelines outlining the safe use of the FTS have been released, including a boxed warning restricting its use to moderate

to severe chronic pain conditions in the opioid-tolerant patient.¹ The US Food and Drug Administration (FDA) also released statements in 2005 and 2007 outlining appropriate prescribing, dose selection, and safe use of the FTS.² In 2012, the FDA approved the extended-release (ER) and long-acting (LA) opioid analgesics risk evaluation mitigation strategy (REMS), and The Joint Commission published a sentinel event alert related to the safe use of opioid analgesics, including the FTS, in the hospital setting.^{3,4}

^{*}Dr. McEvoy was a PGY-2 Drug Information Resident at The University of Kansas Hospital, Kansas City, Kansas, at the time the study was conducted. [†]Medication Safety Coordinator, Department of Pharmacy, The University of Kansas Hospital, Kansas City, Kansas; [‡]Clinical Professor, Emeritus, Department of Pharmacy Practice, University of Kansas, School of Pharmacy Kansas City/Lawrence, Kansas. Corresponding author: Theresa McEvoy, 825 Jadwin Avenue, Suite 250, Federal Building, 2nd Floor, Jonathan M. Wainwright Memorial VA Medical Center, Richland, WA 99352; e-mail: Theresa.mcevoy@va.gov

Several patient characteristics have been associated with an increased risk of severe and fatal ADEs, including lack of opioid tolerance, advanced age, concurrent administration of sedating medications, comorbid respiratory or cardiac conditions, and recent surgical procedures.^{1,4} Fatal respiratory depression may occur even when the FTS is used as recommended in opioid-tolerant patients. Regulatory guidelines therefore restrict use to management of persistent, moderate to severe chronic pain in opioid-tolerant patients requiring continuous administration of opioid analgesics for an extended period of time. Opioid tolerance is defined as receipt of at least 60 mg oral morphine, 30 mg oral oxycodone, or 8 mg oral hydromorphone, or an equianalgesic dose of an alternative opioid analgesic, daily for the preceding 7 days or longer. The FTS is contraindicated in opioid nontolerant patients, patients with impaired pulmonary function, and in patients with other conditions in which the risk of respiratory depression is increased, including use on an as-needed basis and for acute and postoperative pain.¹⁻³

Despite these warnings, reports suggest that the FTS continues to be used inappropriately in opioid-naïve patients to treat acute pain. Serious and fatal adverse events related to the FTS and other opioid analgesics continue to occur.^{5,6} Additionally, fentanyl is considered a high-alert medication at the University of Kansas Hospital (TUKH) and is often implicated in medication event reports. Therefore, the objective of this analysis was to evaluate the inpatient prescribing patterns of the FTS for adherence to recent US regulatory recommendations and to identify the impact of health information technology (HIT) on adherence rates.

METHODS

A retrospective pre- and postintervention analysis was performed on hospitalized patients at TUKH, a regional academic medical center. Patients over 18 years of age admitted to TUKH between January 1, 2012 and May 31, 2013 and receiving a medication order for the FTS were eligible for inclusion. Patients were excluded if there was no documented administration of the FTS within the electronic medical record (EMR). This study was reviewed and approved by the University of Kansas Human Subjects Committee.

Measurements

The primary outcome measure was adherence of FTS medication orders to regulatory recommendations. For medication orders in patients not receiving

the FTS prior to admission (new starts), adherence was defined as a new order in an opioid-tolerant patient (receipt of 60 mg oral morphine or equianalgesic dose of an alternative opioid analgesic for a minimum of 7 days) for use in a moderate to severe chronic pain condition. For medication orders to continue FTS therapy from prior to admission use (continuations), adherent medication orders were defined as an order for the same dose that the patient had been receiving for at least 7 days. This was chosen to ensure tolerance to the documented home dose.

Medication adherence rates were evaluated in preintervention (January 1, 2012 to June 31, 2012) and postintervention (March 15, 2013 to May 31, 2013) cohorts. The intervention consisted of the incorporation of HIT as electronic order instructions and order text questions into electronic medication orders for the FTS (**Figure 1**). Electronic order instructions included text restricting the FTS to use for persistent, moderate to severe pain in opioid-tolerant patients, defined opioid tolerance, and provided equianalgesic dosing for the most commonly prescribed opioids. Additionally, 2 electronic order text questions were added: (1) Is this being ordered for the management of persistent, moderate to severe chronic pain? and (2) Is the patient opioid-tolerant, defined as receiving at least 60 mg oral morphine or equianalgesic dose daily for greater than or equal to 7 days? (**Figure 1**). The ordering provider was to select “yes” or “no (comment provided),” and a space was provided for an explanation of the rationale for ordering outside of the recommended parameters. The order could not be signed electronically until both questions were completed. Ordering providers received education regarding the electronic medication order changes via e-mail prior to initiation of the intervention. Pharmacists received live training at weekly staff meetings. Adherence of FTS medication orders to regulatory recommendations was compared prior to and following inclusion of the electronic medication order instructions and electronic order text questions.

Additional assessment measures included whether sufficient documentation was present upon medication order review to determine adherence of the medication order. In addition, documentation by nursing regarding prior patch location in continuations was collected.

Safety data that were collected included sedation scale rating, respiratory rate, oxygen saturation,

Medications (1 Order)

fentaNYL (DURAGESIC) 25 mcg/hr patch 1 Patch Accept Cancel Link Order Remove

1 Patch, Transdermal, EVERY 72 HOURS, First Dose Today at 1345, Until Discontinued

Order Inst: Transdermal fentanyl is restricted for use in the management of persistent, moderate to severe pain in patients who are opioid tolerant. Opioid tolerance for this purpose is defined as receiving at least 60mg of oral morphine, 30mg of oral oxycodone, 8mg of oral hydromorphone or an equianalgesic dose of another opioid daily for ≥ 7 days.

NOTE: Fentanyl patches should be scheduled Q72H at 0900

Questions:

Prompt	Answer	Comments
1. Is this being ordered for the management of persistent, moderate-severe chronic pain?	Yes No (Comment Provided)	
2. Is the patient opioid-tolerant, defined as receiving at least 60 mg oral morphine or an equianalgesic dose daily for ≥ 7 days?	Yes No (Comment Provided)	

Dose: Patch **1 Patch**

Administer Dose: **1 Patch**

Administer Amount: **1 Patch**

Route: **Transdermal**

Figure 1. Fentanyl transdermal system electronic medication order.

administration of naloxone, and documented ADE in the EMR or internal reporting database.

Statistical Analyses

Categorical variables were analyzed via chi-square and the Fisher exact test. Continuous variables were analyzed via Student *t* test. A *P* value of $< .05$ was considered statistically significant.

RESULTS

A total of 270 FTS medication orders were included in the analysis; 150 and 120 of which were in the preintervention and postintervention cohorts, respectively. The preintervention cohort was evenly divided, with 75 new start and 75 continuation medication orders. The postintervention cohort consisted of 45 new starts and 75 continuations. Baseline characteristics were similar between the preintervention and postintervention cohorts; however, more patients in the postintervention cohort possessed characteristics that increased their risk of ADEs, including increased opioid requirement, post surgery, and current smoker status (Table 1).

Overall adherence to regulatory recommendations was higher in the postintervention cohort as compared to the preintervention cohort (48.7%

preintervention vs 85.0% postintervention; $P < .0001$) (Table 2). Documentation in the EMR was increased as well (76% pre vs 100% post). However, an analysis of the postintervention cohort that evaluated supportive documentation (eg, prior to admission opioid use to determine tolerance) confirmed responses in only 59.2% ($n = 71$) of the EMRs reviewed.

A subgroup analysis to assess adherence to regulatory recommendations in new starts and continuations revealed significantly greater adherence in new starts in the postintervention cohort as compared to the preintervention cohort (34.7% pre vs 73.3% post; $P = .001$); however, adherence was not significantly different for continuations (62.7% pre vs 88.0% post; $P = .673$) (Figure 2). Lack of opioid tolerance was the most frequent reason for not meeting the definition of adherence in new starts (opioid-tolerant patients, 46.7% pre vs 75.6% post; $P = .052$). For continuations, the most frequent reason for failing to meet criteria for adherence was use for fewer than 7 days or undocumented duration of use in the preintervention cohort (65.3% were documented in use for ≥ 7 days) and lack of opioid tolerance in the postintervention cohort (opioid tolerant, 92.0%). No significant differences were found in specific regulatory criteria (Table 3).

Table 1. Baseline inpatient fentanyl transdermal system medication order characteristics

Characteristic	Preintervention (<i>n</i> = 150)	Postintervention (<i>n</i> = 120)	<i>P</i> *
Mean age, years	53.7	55.2	.402
Male, %	43.3	47.5	.494
<i>Risk factors for ADE, %</i>			
Receipt of sedating medications	70.0	58.3	.046
Age > 61 years	33.3	32.5	.885
Pulmonary/cardiac condition	32.0	42.5	.075
Increased opioid requirement	14.7	35.8	<.0001
Post surgery	10.0	30.8	<.0001
Current smoker	10.0	25.8	.001
Sleep apnea	5.3	7.5	.466
Morbid obesity	4.7	9.2	.141
No recent opioid use (new starts only)	5.3	1.7	.615
Pain consult, %	28.0	34.2	.275

Note: ADE = adverse drug event.

*Student *t* test and chi-square test; statistical significance at *P* < .05.

Table 2. Percentage of inpatient fentanyl transdermal system medication orders related to outcome measures

Outcome measures	Preintervention (<i>n</i> = 150)	Postintervention (<i>n</i> = 120)	<i>P</i> *
Adherence to regulatory recommendations	48.7	85.0	< .0001
Inadequate documentation	24.0	0.00	
Documented assessment for patch presence (continuations only)	32.0	42.7	.177
Documented ADE	34.7	23.3	.043

Note: ADE = adverse drug event.

*Chi-square test; statistical significance at *P* < .05.

Figure 2. Percentage of inpatient fentanyl transdermal system (FTS) medication orders adherent to recommended prescribing criteria for new start versus continuation therapy.

Table 3. Percentage of inpatient fentanyl transdermal system (FTS) medication orders adherent to specific prescribing criteria for new starts versus continuation therapy

Medication orders	Preintervention	Postintervention	P*
<i>New start</i>			
No. of patients	75	45	–
Moderate to severe pain	92.0	93.3	.788
Chronic pain condition	78.7	80.0	.862
Postoperative pain	5.3	11.1	.467
Receipt of ≥ 60 mg oral morphine for 7 days	46.7	75.6	.052
<i>Continuation therapy</i>			
No. of patients	75	75	–
Order dose equivalent to home	93.3	92.0	.572
Receipt of FTS for ≥ 7 days (preintervention); opioid tolerant (postintervention)	62.7	92.0	<.0001

*Chi-square test; statistical significance at $P < .05$.

Figure 3. Percentage of inpatient fentanyl transdermal system (FTS) medication orders with documented adverse drug event (ADE).

Significantly fewer documented ADEs occurred in the postintervention cohort as compared to the preintervention cohort (34.7% pre vs 23.3% post; $P = .043$) (Figure 3). The most frequently documented ADEs included sedation (19.3% vs 14.2%; $P = .262$) and respiratory depression (16.7 vs 8.3%; $P = .043$). Rate of administration of naloxone was similar in both cohorts (4.7% vs 3.3%; $P = .582$). Other ADEs included constipation (4.0% vs 5.0%; $P = .692$), altered mental status (2.7% vs 0.0%), hypotension (0.0% vs 0.8%), and bradycardia (0.7% vs 0.0%).

DISCUSSION

This study assessed inpatient FTS medication orders for adherence to regulatory guidelines. Overall medication order adherence was significantly increased in the postintervention cohort following implementation of HIT as compared to the preimplementation cohort (48.7% pre vs 85.0% post).

Initial low adherence rates were largely due to lack of documentation, which was increased in the postintervention cohort (76.0% pre vs 100.0% post). These results suggest that incorporation of HIT into

the medication ordering process may help improve documentation and adherence to regulatory recommendations for use for safe utilization of the FTS and other high-risk medications. Research suggests that preventable medical errors cause patient harm and death in the United States every year⁵ and frequently occur at the ordering stage in the medication use process.⁶ HIT is being implemented and encouraged as a means to improve patient safety and reduce preventable medical errors; however, reports suggest that HIT may also be associated with safety risks and preventable adverse events.⁷⁻⁹

Adherence rates in the present study were consistent with Institute for Safe Medication Practices (ISMP) reports that the FTS continues to be used inappropriately to treat acute pain in opioid-naïve patients.¹⁰ A study performed by Ripamonti et al¹¹ evaluated utilization of the FTS according to the World Health Organization guidelines and the Expert Working Group of the European Association for Palliative Care published guidelines in hospitalized cancer patients in Italy and found that changing therapy to the FTS was inappropriate in as many as 53% of patients.

In the present study, the majority of nonadherent new start medication orders were for non-opioid-tolerant patients (46.7% vs 75.6%). This is consistent with published reports of FTS utilization in opioid-naïve patients. A study performed by Dosa et al¹² determined that 39.3% of nursing home patients newly initiated on long-acting opioids (60.3% of which were FTSs) were opioid-naïve, which was defined as having no documentation of short-acting opioid use in the 60 days preceding initiation. A study performed by Garbe et al¹³ found that 84.5% of German patients newly initiated on the FTS were opioid-naïve, which was defined as no receipt of a high-potency opioid analgesic prescription in the preceding 3 months. Less stringent definitions of opioid tolerance and guidelines for use of the FTS may have contributed to the variable results. Continued use of the FTS in opioid-naïve patients may be due to lack of familiarity with the regulations and conversions between frequently used alternative opioid analgesics.

Lack of documentation of previous opioid use may also contribute to low adherence rates. Nearly one-fourth of all medication orders in the preintervention cohort were lacking the documentation required to assess adherence. The inclusion of HIT increased documentation rates to 100% in the postintervention cohort. Previous opioid use may be captured during the medication reconciliation process. Research suggests that pharmacy-based medication reconciliation

programs may increase the accuracy and reconciliation of medications upon admission and decrease medication errors.^{14,15} The need to maintain and communicate accurate patient medication information via medication reconciliation is included in The Joint Commission National Patient Safety Goals 2014.¹⁶ This helps ensure that future medications are prescribed safely, such as new orders for the FTS.

A potential limitation to the inclusion of electronic order text questions during the ordering process is that the ordering providers may simply answer the question without verifying the accuracy of their response. Documentation confirming the responses to the electronic order text questions was available in only 59.2% of the EMRs reviewed. This may be due to perceived redundancy of documenting supporting information or inaccurate responses.

For continuations, the majority of medication orders that did not meet the definition for adherence were lacking documented duration of use. This was also demonstrated in a study by Jahansouz et al¹⁷ that evaluated pharmacist adherence rates to institutional documentation practices of FTS medication orders and found that only 45.3% of orders continued from outpatient therapy contained documentation for duration of use. Commonly, documentation of patient's prior-to-admission medications provide space to document drug name, dose, frequency, date/time of last dose, and source of information, but do not prompt for duration of use. Providing a space to document duration of use on medication history forms on paper or in EMRs may help encourage inclusion of this information.

The purpose of guidelines for the use of long-acting opioids, including the FTS, is to ensure safe and appropriate use while minimizing the risks of serious and potentially fatal ADEs.^{2,4} In the present study, the occurrence of documented ADEs was significantly lower postintervention. Significantly fewer documented occurrences of respiratory depression occurred despite the significantly higher rate of risk factors in the postintervention cohort. However, administration of naloxone was not significantly affected. This may be due to the low frequency of naloxone administration in both groups. No fatalities related to opioid analgesic use occurred in either cohort. These results suggest that including HIT as order text questions during the medication ordering process may decrease adverse patient outcomes.

There were a number of limitations to the present study. First, the retrospective nature did not allow for assessment of information not documented in the

EMR. Inadequate documentation prevented assessment of nearly a quarter of all preintervention medication orders (24.0%). Additionally, although the inclusion of electronic medication order text questions increased overall adherence rates, only 59.2% of medication orders in the postintervention analysis had sufficient additional documentation in the EMR to confirm adherence. Additional ADEs may have occurred that were not documented in either preintervention or postintervention analysis. Documentation in the EMR may have varied among providers; however, evaluation of a similar time period should have reduced major seasonal variances.

At TUKH, frequent interventions are implemented to increase patient safety and improve patient outcomes. In the interim between the preintervention and postintervention analyses, a transition of care (TOC) initiative was implemented. In October 2012, TUKH's TOC model changed to a primarily pharmacy-driven medication reconciliation process. Utilizing a team approach, pharmacists and medication reconciliation pharmacy technicians are responsible for obtaining medication histories and reconciling medications at all TOC (admission, transfer, discharge). This may have contributed to increases in documentation and adherence rates, as a more thorough medication reconciliation process occurred in the postintervention cohort. This may also have contributed to increased documentation of risk factors in the postintervention cohort.

The time periods of assessment and sample sizes between the analyses were not consistent. Due to the time constraints and coordination required to build the electronic order text questions and help text in the EMR, implementation could not occur until March 2013. Therefore, the duration of postintervention assessment and sample size were not the same as the preintervention assessment. This may have affected the overall results due to variance in prescribing patterns. The small sample size may also have affected the ability to determine a difference between treatment groups.

CONCLUSION

Overall, inpatient FTS medication order adherence to regulatory recommendations was significantly increased following the implementation of HIT via electronic medication order text questions. The postintervention cohort was also associated with a lower rate of documented ADEs, including respiratory depression. A number of medication orders were lacking documentation to fully assess for adherence,

and documentation was increased in the postintervention cohort. These results suggest that incorporation of HIT via electronic order text questions may increase overall adherence rates to regulatory recommendations for safe use, increase documentation rates, and decrease the rate of associated ADEs.

ACKNOWLEDGMENTS

The authors have no conflicts of interest to report.

REFERENCES

1. *Duragesic* [package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; 2012.
2. Information for healthcare professionals: Fentanyl transdermal system (marketed as Duragesic and generics). US Food and Drug Administration Web site. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm084307.htm>. Published December 21, 2007. Updated September 30, 2009. Accessed August 28, 2012.
3. Extended-release (ER) and long-acting (LA) opioid analgesics risk evaluation and mitigation strategy (REMS). US Food and Drug Administration Web site. <http://www.fda.gov/downloads/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm311290.pdf>. Updated July 2012. Accessed August 28, 2012.
4. The Joint Commission. Sentinel Event Alert Issue 49: Safe use of opioids in hospitals. August 8, 2012. http://www.jointcommission.org/sea_issue_49/. Accessed August 28, 2012.
5. Kohn LT, Corrigan J, Donaldson MS. *To Err Is Human: Building a Safer Health System*. Washington, DC: National Academy Press; 2000. <http://www.iom.edu/~media/Files/Report%20Files/1999/To-Err-is-Human/To%20Err%20is%20Human%201999%20%20report%20brief.pdf>. Accessed January 5, 2014.
6. Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. Implications for prevention. *JAMA*. 1995;274(1):29-34.
7. Pederson CA, Gumpfer KF. ASHP national survey on informatics: Assessment of the adoption and use of pharmacy informatics in US hospitals. *Am J Health Syst Pharm*. 2008;65:2244-2464.
8. The Joint Commission. Sentinel Event Alert, Issue 42: Safely implementing health information and converging technologies. December 11, 2008. http://www.jointcommission.org/sentinel_event_alert_issue_42_safely_implementing_health_information_and_converging_technologies/. Accessed January 5, 2014.
9. Blumenthal D. Launching HITECH. *N Engl J Med*. 2010;362:382-385.

10. Cohen MR, Smetzer JL. ISMP Medication Error Report Analysis: Ongoing incidents involving fentanyl patches are alarming!; Insulin concentrate U-500; WHO: dilute vincristine in a minibag. *Hosp Pharm*. 2007;42(10):884-888.
11. Ripamonti C, Fagnoni E, Campa T, et al. Is the use of transdermal fentanyl inappropriate according to the WHO guidelines and the EAPC recommendations? A study of cancer patients in Italy. *Support Care Cancer*. 2006;14(5):400-407.
12. Dosa AM, Dore DD, Mor V, Teno JM. Frequency of long-acting opioid analgesic initiation in opioid-naïve nursing home residents. *J Pain Symptom Manage*. 2009;38(4):515-521.
13. Garbe E, Jobski K, Schmid U. Utilisation of transdermal fentanyl in Germany from 2004 to 2006. *Pharmacoepidemiol Drug Saf*. 2012;21(2):191-198.
14. Smith SB, Mango Md. Pharmacy-based medication reconciliation program utilizing pharmacists and technicians: A process improvement initiative. *Hosp Pharm*. 2013;48(2):112-119.
15. Murphy EM, Oxencis CJ, Klauck JA, et al. Medication reconciliation at an academic medical center: Implementation of a comprehensive program from admission to discharge. *Am J Health Syst Pharm*. 2009;66(23):2126-2131.
16. National Patient Safety Goals effective January 1, 2014. http://www.jointcommission.org/assets/1/6/HAP_NPSG_Chapter_2014.pdf. Accessed February 23, 2014.
17. Jahansouz F, Hsiao J, Dhillon K, et al. Pharmacist documentation of fentanyl patch orders in an academic medical center. *Hosp Pharm*. 2011;46(11):854-863. ■