Application of Software Design Principles and Debugging Methods to an Analgesia Prescription Reduces Risk of Severe Injury From Medical Use of Opioids

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A prescription is a health-care program implemented by a physician or other qualified practitioner in the form of instructions that govern the plan of care for an individual patient. Although the algorithmic nature of prescriptions is axiomatic, this insight has not been applied systematically to medication safety. We used software design principles and debugging methods to create a "Patient-oriented Prescription for Analgesia" (POPA), assessed the rate and extent of adoption of POPA by physicians, and conducted a statistical process control clinical trial and a subsidiary cohort analysis to evaluate whether POPA would reduce the rate of severe and fatal opioid-associated adverse drug events (ADEs). We conducted the study in a population of 153,260 hospitalized adults, 50,576 (33%) of whom received parenteral opioids. Hospitalwide, the use of POPA increased to 62% of opioid prescriptions (diffusion half-life = 98 days), while opioid-associated severe/fatal ADEs fell from an initial peak of seven per month to zero per month during the final 6 months ($P < 0.0016$) of the study. In the nested orthopedics subcohort, the use of POPA increased the practice of recording pain scores (94% vs. 72%, $P < 0.00001$) and the use of adjuvant analgesics (95% vs. 40%, $P < 0.00001$) and resulted in fewer opioid-associated severe ADEs than routine patient-controlled analgesia (PCA) (0% vs. 2.7%, number needed to treat (NNT) = 35, $P < 0.015$). The widespread diffusion of POPA was associated with a substantial hospitalwide decline in opioid-associated severe/fatal ADEs.

Hospitalized patients are subjected to an average of more than one medication error each day;[1] adverse drug events (ADEs) cause more than 770,000 patient injuries or deaths annually in US hospitals (http://www.ahrq.gov/qual/aderia/aderia.htm); an estimated 30–40% of patients receive health care inconsistent with the available scientific evidence; and 20–25% of patients receive health care that is either unnecessary or actually harmful.[2] Among hospitalized adults, opioid ADEs are more common than any other class[3] and are disproportionately severe: opioid-associated respiratory depression accounts for only 2% of hospital ADEs but 12.3% of life-threatening ADEs[4] and 25% of fatal ADEs.[5]

We hypothesized that the application of software design principles and debugging methods to a prescription would reduce the rate of severe and fatal ADEs. To test this hypothesis, we created and debugged a "Patient-oriented Prescription for Analgesia" (POPA; **Figure 1**), assessed the rate and extent of its adoption by physicians, and conducted a statistical process control clinical trial and subcohort analysis in hospitalized adults.

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Received 27 June 2007; accepted 22 January 2008; advance online publication 19 March 2008. doi:10.1038/clpt.2008.24

Patient–oriented Prescription for Analgesia (Adult Program)

Date & Time_____ Procedure/Cause of Pain_____

Note: To override default values (in parentheses), enter substitute values in spaces. Default values are for adults weighing more than 40 kg. To delete an order, cross it out & initial.

DISCONTINUE all previous Opioids, Benzodiazepines, Antiemetics, & NSAIDs

Adjuvant Analgesia (Check one of the following options)

☐ **NSAID Option:** First dose only: **Ketorolac(Toradol)** i.v. or subcut. (15)_____mg, & then
- If unable to take oral meds: **Ketorolac** i.v. or subcut. (15)_____mg every 6 hrs. STOP after 3 days.
- If able to take oral meds: **Ibuprofen** p.o. (600)_____mg every 6 hrs. STOP after (3)_____days.

☐ **Non-NSAID Option:** **Acetaminophen** rectally or p.o. (975)_____mg every 6 hrs.

Programmed Opioid Analgesia for Abbott PCA Model 4100 (Checking box activates full protocol)

☐ **Fentanyl** 50 micrograms/mL by subcutaneous (subcut.) infusion with portless PCA tubing through 0.22 micron in-line filter.

Set–up

- Initial Dose: If this protocol is started in PACU, follow anesthesiologist's post-surgical orders while patient in PACU. If started on floor & if pain score is 8 cm or greater, give (50)_____micrograms subcut, *one dose only.*
- Continuous: (25)_____micrograms/hr (If left blank, dose defaults to 25 micrograms/hr.) DO NOT INCREASE continuous **Fentanyl** dose rate more often than once every 24 hours.
- PCA (On-demand): (25)_____micrograms (If left blank, dose defaults to 25 micrograms with each patient demand.)
- Lockout: 15 min
- 4 Hour Dose Limit: 75% of (Continuous + On-demand doses) *Adjust 4 hour dose limit whenever dose changes.*

- *Breakthrough pain:* If pain score is 8 cm or greater, INCREASE on-demand dose by (10)_____micrograms; reassess in 1 hour. Repeat 3 times. If pain score is 8 cm or greater on 3 consecutive assessments then notify physician.
- *Taper.* STOP on-demand dose after (3 days)_____(Alternatively, enter a stop date) *& then* REDUCE continuous dose rate every 4 hours by (10)_____micrograms.
- *Minimal pain:* If the visual analogue pain score is 2 cm or less on any 3 consecutive assessments, REDUCE on-demand dose by (10)_____micrograms.
- *Oversedation:* If oversedated, hold continuous & on-demand **Fentanyl** doses for 4 hrs, then restart continuous **Fentanyl** at 1/2 prior dose rate & on–demand **Fentanyl** at 1/2 prior dose; reassess at 1 hour & 2 hours. If unarousable or respiration depressed, (e.g., resp. rate less than 6/min or O2 saturation less than 92%), then STOP **Fentanyl** & give **Naloxone(Narcan)** 0.1 mg i.v. every 2–5 mins up to 4 times until awake. Notify physician *after* giving first dose of naloxone.
- *p.r.n. Constipation:* **PEG Standard Solution (Miralax)** p.o. 240 mL p.r.n. once daily when tolerating fluid diet. **Senna Standard Extract** p.o. 1 to 4 tablets p.r.n. twice daily when tolerating fluids.
- *p.r.n. Nausea:* Mild nausea: **Metoclopramide (Reglan)** i.v. or subcut. 5 to 10 mg p.r.n. every 8 hrs. Severe nausea or vomiting: **Droperidol (Inapsine)** i.v. or subcut. 1.25 to 2.5 mg p.r.n. every 8 hrs. If patient continues to vomit 2 hours after receiving Droperidol then notify physician.
- *p.r.n. Pruritis:* **Diphenhydramine (Benadryl)** subcut., i.v., or p.o. 10 to 25 mg p.r.n. every 8 hrs.

Monitoring Orders

Use a 10 cm. Visual Analogue Pain Scale (such as CAT Pain Gauge) for all pain assessments; do not substitute alternate scale.
Measure & Record Visual Analogue Pain Score with each vital sign recording; reassess 1 hour after each fentanyl dose change.
Cutaneous O_2 saturation measures every 4 hours while patient lethargic or sleeping.

Patient–oriented Prescription for Analgesia (Adult Program) v1.1 Revised 20 September 2001

Physician's ID # *Physician's Signature*

Figure 1 Patient-oriented Prescription for Analgesia (Adult Program) v1.1 after debugging. This is the current version of POPA. The CAT pain scale mentioned in "monitoring orders" is a mechanical visual analog pain scale manufactured by Caterpillar. (Although the protocol specifies droperidol, prochlorperazine was substituted for droperidol after a Food and Drug Administration–mandated addition of a black box warning to the droperidol package insert.)

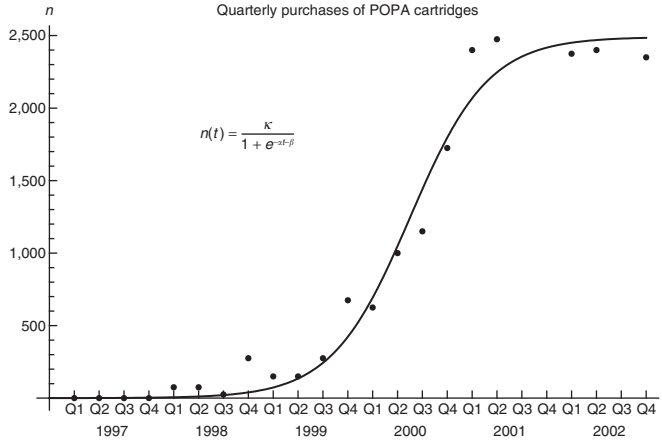


Figure 2 Diffusion of Patient-oriented Prescription for Analgesia (POPA) in the hospital and effect on opioid-associated severe/fatal adverse drug events. This shows the optimal fit of the logistic growth equation to quarterly hospitalwide purchases of POPA cartridges. These empty glass and silicone rubber patient–controlled analgesia pump cartridges were filled with fentanyl solution by our pharmacy and used solely for POPA. The diffusion half-life of the use of POPA in hospital prescriptions was 98 days.

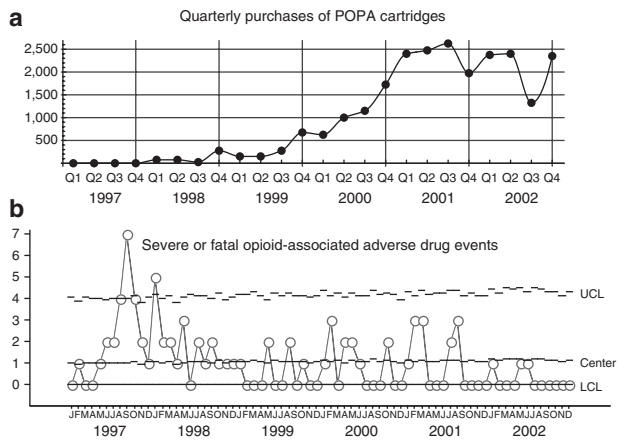


Figure 3 Diffusion of Patient-oriented Prescription for Analgesia (POPA) in the hospital and effect on opioid-associated severe/fatal adverse drug events (ADEs). (**a**) Quarterly hospitalwide purchases of POPA cartridges over time. (**b**) A u-type process control run chart ($\sigma = 3$) for hospitalwide opioid-associated severe/fatal ADEs. As the use of POPA became more widespread, opioid-associated severe/fatal ADEs became less common. LCL, lower control limit; UCL, upper control limit.

RESULTS

Diffusion of POPA use among prescribers

POPA is the prescription shown in Figure 1. The hospitalwide diffusion half-life for adoption of POPA by prescribers was 98 days (Figures 2 and 3a). By the end of the study period, POPA accounted for 62% of all parenteral opioid prescriptions hospitalwide.

Statistical process control trial in full cohort of hospitalized adults

During the study period, 4,453 ADEs were reported, including 503 opioid-associated ADEs above the causality threshold (Naranjo score > 4), 74 of which were severe and three of which were fatal. The run chart showed two transitions, first from an out-of-control process to an in-control process, then to an in-control process with a lower central tendency (Figure 3b). Event rates were higher than the upper control limit during 3 months in 1997, indicating special causes of variation—identified as opioid polypharmacy, failure to reduce opioid dose during oversedation or respiratory depression, and inappropriate meperidine use. Between 1998 and 2002, there was a reduction in the frequency of these special causes of variation, leading to the opioid ADE rate remaining within control limits. The increasing use of POPA and its subroutines in the full hospital cohort was associated with a decline over time in severe/fatal opioid-associated ADEs, from a peak of seven events per month in September 1997 to a rate consistently below the run chart centerline for the final 16 consecutive months ($P < 0.0037$), and eventually falling to zero events per month for the final 6 consecutive months of the study ($P < 0.0016$).

The substantial decline in the rate of severe/fatal opioid-associated ADEs does not correspond to zero risk, because adherence to POPA safety practices was not universal (Table 1) and unidentified hazards may remain. The fall in the rate of opioid-associated severe/fatal ADEs is unlikely to be a result of performance expectation (Hawthorne effect)[6] given the consistency, magnitude, and sustained duration of this decline across all hospital services, the accompanying 45% decline in the use of opioids, the increase in adjuvant analgesic drug use, and the increased frequency of assessment of pain severity, hemoglobin oxygen saturation, and level of consciousness. There were no severe or fatal ADEs associated with the adjuvant analgesics ketorolac, ibuprofen, and acetaminophen, consistent with prior reports that risk of ketorolac-associated gastrointestinal bleeding or acute renal failure is negligible at doses <150 mg/day given for <5 days.[7,8] The run charts for antibiotics and anticoagulants/thrombolytics—drug classes for which there had been no specific medication safety improvement effort—showed no decrease in severe/fatal ADEs over the same interval (Figure 4, middle and bottom panel, respectively).

As measured in fentanyl equivalents (FEs), hospitalwide use of all parenteral opioids, including fentanyl, hydromorphone, morphine, and meperidine (Table 2) showed an initial rise from 48 g FE in 1997 to a peak of 73.4 g FE in the year 2000, coinciding

Table 1 Attributes of patients, type of surgery, pain management, and outcomes in the nested cohort of 496 orthopedic surgery patients

Univariates	PCA (N = 245)	POPA (N = 251)	Difference (95% CI)	PV (%)	ESS (%)	P value
Patient attributes						
Mean age (years)	63.3	65.5	2.2 (0.1 to 4.3)	12	12	$P < 0.027$*
Mean weight (kg)	90.3	90.6	0.3 (−3.7 to 4.3)	—	—	$P < 0.92$
Female (%)	157 (61.1)	150 (59.8)	−1.3 (−9.8 to 7.2)	—	—	$P < 0.99$
Male (%)	100 (38.9)	101 (40.2)	1.3 (−7.2 to 9.8)	—	—	$P < 0.99$
Surgery						
Knee surgery (%)	173 (67.3)	148 (59.0)	−8.4 (−17 to 0.001)	9.0	8.4	$P < 0.062$
Hip surgery (%)	84 (32.7)	103 (41.0)	8.4 (−0.001 to 17)	9.0	8.4	$P < 0.062$
Bilateral surgery (%)	33 (12.8)	19 (7.6)	−5.3 (−10.5 to 0.0)	14	5.1	$P < 0.072$
Surgical revision (%)	36 (8.6)	35 (8.6)	0 (−6.0 to 6.0)	—	—	$P < 0.90$
Pain management						
Pain scored (%)	186 (72.3)	234 (93.6)	21.2 (15 to 27)	38	22	$P < 0.00001$**
Adjuvant analgesic (%)	103 (40.4)	239 (95.2)	55.1 (48.6 to 61.7)	63	55	$P < 0.00001$**
Pain scored and adjuvant analgesic (%)	77 (30)	224 (89.2)	59.3 (52 to 66)	62	59	$P < 0.00001$**
Outcomes						
Severe/fatal ADE (%)	7 (2.7)	0 (0)	−2.7 (−4.7 to −0.7)	51	51	$P < 0.0077$**
Pain score (0–10)	4.5	4.7	0.1 (-0.4 to 0.6)	—	—	$P < 0.18$
Nausea (%)	121 (47.1)	110 (43.8)	−3.3 (−11.9 to 5.3)	—	—	$P < 0.47$
Length of stay (days)	4.3	4.2	−0.13 (−0.46 to 0.20)	—	—	$P < 0.27$

Patients given POPA were demographically similar to patients given routine PCA, were more likely to have a recorded pain score and more likely to get an adjuvant analgesic, and were less likely to have a severe ADE. Mean pain scores, rate of nausea, and duration of hospitalization were similar. Compared with routine morphine PCA, use of POPA was associated with significantly fewer severe/fatal ADEs. Compared with hip surgery or bilateral knee surgery, unilateral knee surgery was a significant predictor of opioid-associated severe ADE; we had made no a priori hypothesis regarding the effect of type of surgery on risk. ESS, measure of effect strength for sensitivity (0 = chance, 100 = perfect intergroup discrimination);[8] type I error rate is exact (permutation) P value estimated via 10,000 Monte Carlo experiments.[8]

ADE, adverse drug event; PCA, patient-controlled analgesia; POPA, Patient-oriented Prescription for Analgesia; PV, predictive value achieved by the analysis.[8]

*Statistically significant but unstable in jackknife validity analysis. **Statistically significant and stable in jackknife validity analysis.

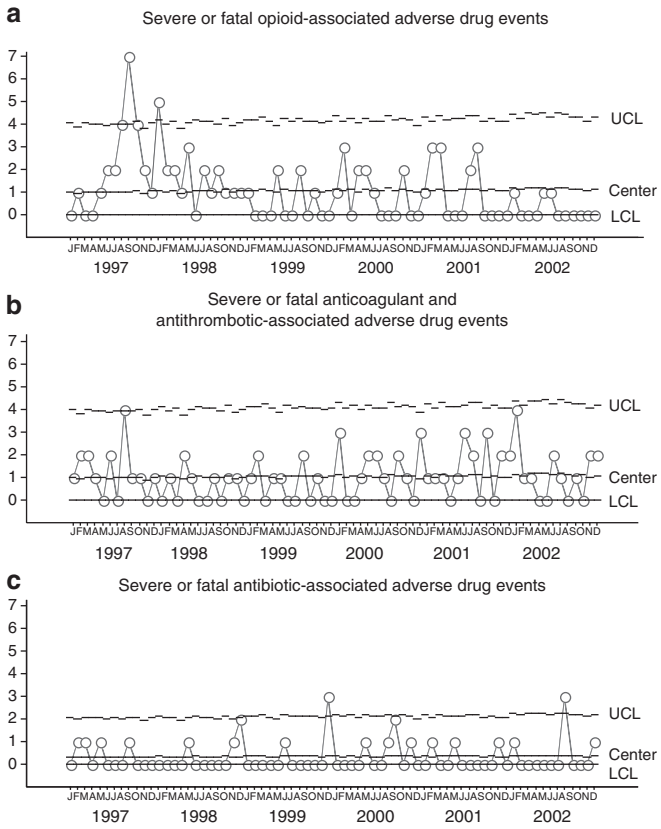


Figure 4 Comparison of trends in the rates of occurrence of severe/fatal adverse drug events (ADEs) associated with (**a**) opioids, (**b**) thrombolytics/anticoagulants, and (**c**) antibiotics. The increasing use of Patient-oriented Prescription for Analgesia (POPA) and its subroutines in the hospital cohort was associated with a statistically significant decline in severe/fatal opioid-associated ADEs. By way of comparison, there were no statistically significant changes in the rates of severe/fatal ADEs associated with anticoagulants/thrombolytics or with antibiotics over the same period. LCL, lower control limit; UCL, upper control limit.

Table 2 Trends in annual hospitalwide parenteral opioid use in grams of fentanyl equivalents

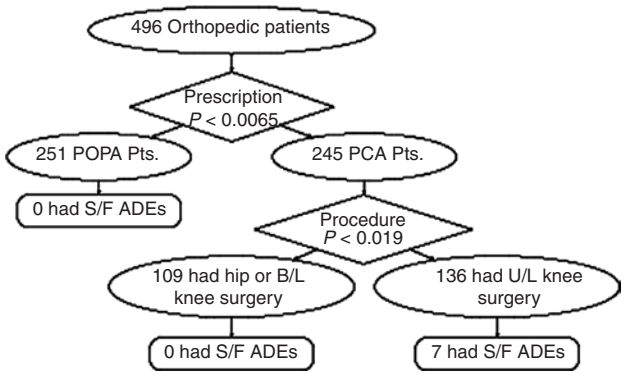
	Annual opioid use in grams of fentanyl equivalents				
Year	Fentanyl	Morphine	Hydromorphone	Meperidine	Total
1997	9.3	33.4	1.0	4.4	48.0
1998	10.9	36.4	1.3	4.6	53.2
1999	13.6	36.7	0.8	4.5	55.5
2000	17.2	51.9	1.5	2.8	73.4
2001	16.6	17.3	3.9	1.3	39.2
2002	21.2	15.2	2.8	1.4	40.7

As measured in fentanyl equivalents, hospitalwide use of all parenteral opioids, including fentanyl, hydromorphone, morphine, and meperidine, showed a rise from 1997 to 2000, coinciding with an effort to improve the efficacy of pain management, and then a fall from 2000 to 2002, coinciding with the rapid diffusion of POPA use among prescribers, a consequent displacement of morphine and meperidine by fentanyl and a generalized reduction of opioid doses on account of coadministration of adjuvant ketorolac, ibuprofen, and acetaminophen. As POPA uses fentanyl exclusively, the increasing use of POPA resulted in the increasing use of fentanyl in the hospital. Opioids were given both as discrete doses and as continuous infusions. A typical discrete dose of fentanyl is 25 μg. Therefore, the 21.2 g of fentanyl dispensed in 2002 would correspond to 848,000 discrete doses of 25 μg of fentanyl.

POPA, Patient-oriented Prescription for Analgesia.

Table 3 Outcomes (severe/fatal adverse drug events) and risk factors in the nested cohort of 496 orthopedic surgery patients given either POPA or routine morphine PCA

Risk factor for S/F ADE	PV (%)	ESS (%)	*P* value
Univariable optimal discriminate analysis			
Use of PCA instead of POPA	51	51	$P < 0.0069$*
Knee surgery vs. hip surgery	51	37	$P < 0.049$*
Unilateral surgery	—	—	$P < 0.63$
Unilateral knee surgery	51	47	$P < 0.030$*
Revision surgery	—	—	$P < 0.99$
Nausea (Y/N)	—	—	$P < 0.71$
Maximum pain score day 1 (0–10)	—	—	$P < 0.63$
Pain not scored	—	—	$P < 0.61$
Multiple opioids prescribed	—	—	$P < 0.68$
Adjuvant analgesic omitted	51	40	$P < 0.037$*
Pain not scored OR adjuvant analgesic omitted	51	46	$P < 0.017$*
Weight (kg)	52	55	$P < 0.019$**
Sex	—	—	$P < 0.25$
Age	—	—	$P < 0.30$
Length of stay (days)	—	—	$P < 0.53$
Classification tree analysis			
Overall model	53	73.1	$P < 0.04$***
Use of standard PCA instead of POPA node	51	51	$P < 0.0065$†
Unilateral knee surgery node	5.3	45	$P < 0.019$†



Patients being managed with POPA had a significantly lower rate of opioid-associated severe/fatal ADEs than did patients on routine PCA. Statistical results are reported as mean values or percentages (for ordered and categorical attributes, respectively). Calculations of the predictive value, effect strength for sensitivity (ESS), and generalized exact (permutation) *P* value were based on the resultant optimal discriminant analysis (ODA) model. ESS is a normed statistic on which 0 = discrimination expected by chance, and 100 = perfect intergroup discrimination. All reported *P* values are nondirectional. Type I error rate (*P* value) is an exact (permutation) *P* estimated through 10,000 Monte Carlo experiments. The optimal classification tree analysis (**Table 1**) employs both the classical nondirectional Fisher's exact test[58] and resampling calculations.

ADE, adverse drug event; PCA, patient-controlled analgesia; POPA, Patient-oriented Prescription for Analgesia; Pts., patients; PV, predictive value achieved by the analysis; S/F ADE, severe/fatal ADE.

*Statistically significant and stable in jackknife validity analysis.[56] **Statistically significant but unstable in jackknife validity analysis.[56] ***Statistically significant by sequentially rejective Sidak Bonferroni–type procedure for multiple comparisons. †Statistically significant by nondirectional Fisher's exact test.[57]

Table 4 Severe opioid-associated ADEs in a nested cohort of orthopedic patients treated with PCA

Sex	Age	Wt (kg)	Adjuvant analgesic	Pain score	LOS	ADE description	Outcome
F	68	73	No	Yes	3	Respiratory arrest	Naloxone, full recovery
F	39	99	No	Yes	3	Respiratory arrest (O_2 Sat. 83%)	Naloxone, full recovery
F	71	109	No	Yes	4	Respiratory depression (O_2 Sat. 66%)	Naloxone, full recovery
F	61	125	Yes	Yes	4	Respiratory depression	Naloxone, full recovery
F	56	136	Yes	No	6	Respiratory depression, mechanical ventilation, (O_2 Sat 85%)	PCA D/Ced, full recovery
F	48	136	No	No	4	Respiratory depression, mechanical ventilation	PCA D/Ced, full recovery
M	61	186	No	Yes	30	Respiratory arrest, airway obstruction	Cerebellar infarction, ataxia

Each of these seven life-threatening events among routine morphine PCA orthopedic patients had a Naranjo score >4. There were no severe or fatal events in patients treated with POPA. Only one of the seven patients with a severe opioid-associated ADE had both a recorded pain score and was given an adjuvant analgesic. There were no severe or fatal ADEs associated with drugs other than opioids in the orthopedic surgery cohort.

ADE, adverse drug event; LOS, hospital length of stay in days; PCA, patient-controlled analgesia; POPA, Patient-oriented Prescription for Analgesia.

with an effort to improve the efficacy of pain management, and then fell by 45% to 40.7 g FE in 2002, coinciding with the rapid diffusion of POPA use among prescribers, displacement of morphine and meperidine by fentanyl, and a generalized reduction of opioid use due to coadministration of the adjuvant analgesic drugs ketorolac, ibuprofen, and acetaminophen. As POPA uses fentanyl exclusively, the increasing use of POPA resulted in increasing use of fentanyl in the hospital, from 9.3 g in 1997 to 21.2 g in 2002 (**Table 2**). Of the 77 opioid-associated ADEs, there were 2 fatal and 11 severe meperidine-associated ADEs. Eight of these thirteen meperidine-associated events were characterized by seizures or psychosis due to accumulation of the toxic metabolite normeperidine in patients with diminished kidney function. Over the study period, use of ketorolac increased by 71%, use of meperidine declined by 69%, and the recording of at least one pain score increased from <1 to >50% of the patients. Even when not explicitly prescribed, there was a notable increase in the use of adjuvant analgesics, sedation monitoring, and pain scoring for non-POPA patients—particularly in hospital units where POPA was used extensively. However, this informal use remained less prevalent than the formal use of these safety practices among POPA patients (**Table 1**).

Exposure–effect optimal discriminant analysis in orthopedic surgery cohort

The 251 POPA patients and 245 routine morphine patient-controlled analgesia (PCA) patients were demographically similar (**Table 1**), and were in a single hospital unit staffed by the same nurses and pharmacists, and were attended by the same surgeons. POPA patients were more likely to have their pain scores recorded (94% vs. 72%, NNT = 4.7) and to be given round-the-clock adjuvant analgesia (95% vs. 40%, NNT = 1.8, **Table 1**). Patients given round-the-clock adjuvant analgesia were less likely to have a severe opioid-associated ADE ($P < 0.037$, **Table 3**). POPA patients were less likely than routine morphine PCA patients to have a severe opioid-associated ADE (0/251 vs. 7/245, $P < 0.007$, NNT = 35, **Table 3**). No POPA patient required resuscitation with the opioid antagonist naloxone or had hemoglobin saturation measurements <92%. Of the seven orthopedic surgery patients with severe opioid-associated ADEs, six were women, five were morbidly obese, all had unilateral knee surgery, only one had both a recorded pain score and received an adjuvant analgesic, and none had been treated with POPA (**Table 4**).

In multivariate analysis a strong, statistically significant two-variable classification tree model consisting of analgesia prescription (routine morphine PCA vs. POPA) and the type of surgical procedure (unilateral knee surgery vs. hip surgery or bilateral knee surgery) emerged for prediction of severe opioid-associated ADEs. Analgesia prescription (morphine PCA) was the first attribute loading in the classification tree model, and the type of surgical procedure (unilateral knee surgery) was the second attribute loading. Effect strength for sensitivity is a standardized measure of effect strength, where 0 = chance and 100 = perfect intergroup discrimination. For this model, effect strength for sensitivity was 73.1%, indicating a very strong signal. The individual components of the model were statistically significant by Fisher's exact test and the type I error rate of the overall model was confirmed as statistically significant ($P < 0.04$, **Table 3**) using a sequentially rejective Sidak Bonferroni–type procedure for multiple comparisons.

DISCUSSION

Physicians usually rely on memory and write extemporaneous prescriptions. Occasionally, physicians use standard order sets or templates,[9–11] but these are rarely derived explicitly and precisely from scientific evidence,[12,13] often violate principles of good software design, and are not verifiably debugged. Standard order sets or templates have been shown to improve compliance with drug therapy recommendations in some settings[14] but not in others.[15] Prescription bugs in standard order sets can cause catastrophic medication errors.[16] We are unaware of any earlier study of the effects of prescription design and debugging on patient outcomes.

The apparent simplicity of prescriptions is deceptive, as the prescriber's terse instructions rely implicitly on subroutines: toxicity and efficacy monitoring, pharmaceutical compounding, pharmacy and nursing practices, operating instructions, laboratory methods, and standard operating procedures. Neglect of scientific evidence, poor design, and lack of adequate debugging of prescriptions and their subroutines likely account for their erratic and occasionally fatal effects. The recognition of the algorithmic nature of prescriptions compels the application of software

design principles and debugging methods to their improvement.[17] Competent programmers begin with detailed software specifications, write modular, reusable code,[18] and devote substantial time and effort to debugging.[19] Developing Computerized Physician Order Entry (CPOE) software with the understanding that prescriptions are programs and not mere text, may lead to improved drug therapy performance in terms of safety, efficacy, and cost.

There has been no method to ensure the rapid, reliable translation of detailed knowledge about drug safety, efficacy, and cost into clinical practice. Clinical practice guidelines have been variously criticized as being vague, untested, nonrigorous,[20] obsolescent,[21] and largely ignored by physicians.[22] Physician education alone does not improve patient safety.[23] There is little evidence that crew resource management training through simulation reduces the rate of medication errors.[24] CPOE may increase the error rate[25] and may not reduce the rate of ADEs when the prescriptions contained in the CPOE system are not properly designed and debugged.[26] Hospital quality-assurance programs may identify many drug therapy flaws, but often fail to translate this knowledge into improved practice.

It is possible for a physician to order drug therapy without consulting relevant research articles, clinical practice guidelines, expert opinions, textbooks, or lectures. However, a physician cannot order drug therapy without a prescription. The prescription is located on the critical path between intent and practice. Well-formed, widely used prescriptions exert beneficial effects through reduction of clinical process variation, familiarity to clinicians, and displacement of unsafe or ineffective practices. When properly designed and debugged, prescriptions provide a conduit through which evidence-based medical knowledge can reliably reach patients. Our experience has been that clinicians who use these prescriptions provide assiduous peer review, compelling the translation of new medical knowledge into improved prescriptions.

We have shown here that sound prescription design followed by iterative cycles of hazard identification and debugging can reduce the rate of severe patient injury by eliminating prescription bugs that are a root cause of opioid-associated ADEs. As POPA does not depend on resources that are unique to our hospital, we expect that POPA is widely applicable. The new discipline of algorithmic medicine we introduce here provides a conceptual basis for surmounting the intransigent implementation barriers that impede translation of medical knowledge into clinical practice.

METHODS

The setting is OSF Saint Francis Medical Center (Peoria, IL), a 731-bed tertiary care academic medical center and the primary teaching hospital for the University of Illinois College of Medicine at Peoria. The principal experiment is a statistical process control trial in the cohort consisting of all 153,260 adults (18 years or older) hospitalized from January 1997 to December 2002, 50,576 (33%) of whom received parenteral opioids. The exposure variable is monthly POPA usage over the interval January 1997 to December 2002. The effect variable is the monthly hospitalwide number of severe and fatal opioid ADEs during the interval January 1997 to December 2002.

The subsidiary experiment is a cohort study of 496 orthopedic surgery patients, consisting of all 251 patients who were prescribed POPA and all 245 patients who were prescribed routine intravenous morphine PCA during the study period. For the univariate analyses, the effect variable is the number of severe or fatal opioid ADEs. The exposure variables are analgesia prescription (POPA vs. morphine PCA), procedure (unilateral knee surgery, bilateral knee surgery, unilateral hip surgery, or bilateral hip surgery), weight, age, sex, revision surgery vs. initial surgery, use of visual analog pain scale, use of adjuvant analgesics, use of multiple opioids, pain score, nausea, and length of hospital stay (**Table 1**). We also identified a multivariate model for prediction of severe/fatal opioid-associated ADEs.

Software design and debugging of POPA. The design and debugging of POPA was informed by literature reports of opioid-associated hazards, errors, and defects, and by failure mode, effect, and criticality analysis (http://www.jcaho.org/accredited+organizations/patient+safety/fmeca/) of events in our hospital. The most common bugs in non-POPA analgesia prescriptions in our hospital were: failure to monitor patient oxygenation and level of consciousness, failure to reduce opioid dose in the presence of respiratory depression or oversedation, omission of a round-the-clock adjuvant analgesic, omission of pain severity assessments, failure to prompt opioid dose escalation for uncontrolled pain, simultaneous use of multiple opioids, simultaneous use of opioids and other sedating drugs, and inappropriate use of meperidine.

We have earlier described[27] our use of the balanced-scorecard method[28] to manage the tradeoffs between important drug therapy outcomes. For example, concern about opioid-associated ADEs may cause underdosing and inadequate analgesia.[29] The balanced scorecard for POPA includes the parameters severe/fatal ADE rate, visual analog pain score, duration of hospitalization, and adoption rate of POPA by prescribers. The software specification for POPA required a decrease in severe/fatal ADEs with no offsetting increase in pain scores or duration of hospitalization.

Our first design goal for POPA was to improve the detection of and response to patient oversedation and respiratory depression by implementing periodic assessments of respiratory rate, cutaneous hemoglobin O_2 saturation, and level of consciousness. In POPA, these assessments are linked to explicit criteria prompting opioid dose reduction. A mechanical visual analog pain scale[30] was specified to identify patients requiring opioid dose changes. Our second design goal was to increase the use of round-the-clock adjuvant analgesia, with parenteral ketorolac,[31,32] oral ibuprofen,[33] or oral or rectal acetaminophen,[34] as coadministration of these drugs reduces the required opioid dose and the consequent risk of respiratory depression. Our third design goal was to displace unsafe opioids such as meperidine with fentanyl. Fentanyl is a synthetic, high potency opioid with high lipid solubility, a rapid intercompartmental clearance, no active or toxic metabolites, high μ_1-opioid selectivity, lack of tissue irritation, and minimal myocardial depressant or vasodilatory effects. The pharmacokinetic properties of fentanyl minimize hysteresis between dose and effect, facilitating titration of demand[35] and basal[36] fentanyl doses, thereby minimizing mismatch of pain severity and opioid effect. Fentanyl has been underused among hospitalized adults because of the lack of a suitable algorithm.

Other notable features of POPA include administration of fentanyl through the subcutaneous route, use of a basal continuous fentanyl dose, avoidance of drugs that interact with fentanyl, and nested control loops for fentanyl dosing—an inner loop of on-demand PCA, and an outer loop of nurse-adjusted fentanyl dose based on assessment of pain and oversedation. The subcutaneous route is more easily established and reliably maintained than the intravenous route, avoiding the severe pain or oversedation that can occur when loss of intravenous access requires *ad hoc* intramuscular or oral opioid administration. Subcutaneous fentanyl is safe, effective, and has pharmacokinetics similar to intravenous administration.[37–40] The use of a basal continuous fentanyl dose provides an "opioid floor," avoiding severe pain when there are long intervals between on-demand doses, as occur during sleep. Using an established model[41] over a range of pharmacokinetic parameter values, we ran simulations[42] of fentanyl kinetics after subcutaneous administration[43] to determine default fentanyl dose and dose increments for POPA. The default fentanyl doses are 25 μg/h continuous and 25 μg as per demand, with a lockout time of 15 min and a 4-h dose limit of 75% of the unlimited

maximal dose. Subcutaneous fentanyl PCA was administered through an Abbott PCA Model 4100 pump (Abbott Laboratories, North Chicago, IL), a 0.22 μm inline filter, and a Sof-set subcutaneous catheter.

All prescriptions (physicians' orders) in our hospital were either handwritten or verbal. POPA prescriptions were ordered on a standard paper form (**Figure 1**). We performed an additional comparative assessment of POPA in the orthopedic surgery subcohort because there had been a high preintervention rate of opioid ADEs among these patients. The routine morphine PCA protocol used as a comparator for this assessment was an established practice at our medical center, was based on a widely accepted protocol,[44] and also was ordered on a standard form.

POPA was tested and refined in clinical scenarios with experienced clinicians and during treatment of 250 patients in five debugging cycles, using direct observation, clinician interviews, and medical record reviews to identify and eliminate prescription bugs. Nurses often omitted evaluation of patient's pain, oxygenation, and sedation in other opioid prescriptions because of their perception that these evaluations did not improve patient safety or comfort. Thus, POPA provides explicit instructions whereby the nurse can use their evaluations to adjust fentanyl dosing or take other appropriate action. Conventional dose titration of opioids requires physician–nurse or physician–pharmacist communication for each dose change, often resulting in long delays. With POPA, dose titration occurs with minimal delay, lessening the risk of a mismatch between pain severity and opioid dose.

Other POPA bug fixes during these debugging cycles included extensive editing of POPA text for accuracy and clarity based on direct observation of clinical encounters and on clinician feedback, use of defaults to avoid ambiguity when a prescriber does not specify an initial value, and protocols to transition between POPA and other opioid prescriptions. In software design terms, POPA is modular, has well-defined interfaces, and minimizes tight coupling (**Figure 1**). For example, by default, the first order in POPA discontinues previously prescribed opioids, benzodiazepines, and other sedatives, as to avoid interactions with fentanyl.

Implementation of POPA. We established the baseline 12 months prior to introduction of POPA by disseminating information about analgesia safety and efficacy to clinicians through established channels, including one-on-one discussions, conferences, grand rounds, department and committee meetings, newsletters, brochures, and practice guidelines.

We established the intervention by providing education and training about POPA to all nurses, physicians, and pharmacists through brief in-service training sessions and distribution of supportive written materials. POPA was then made available to prescribers, who were free to choose POPA or other analgesia prescription at their discretion. Analgesia management for both POPA and routine analgesia was provided by the primary service and not by a special analgesia service.

Evaluation of POPA. We chose a statistical process control trial design instead of a randomized controlled trial design because statistical process control trials have greater statistical power, are more ethically acceptable when the beneficial effect of the test article has high plausibility, require fewer resources, are minimally disruptive of clinical practice, cause less distortion of underlying clinical processes, and are less susceptible to null bias.[45–49] Also, the Deming–Shewart plan-do-study-act loops (http://deming.eng.clemson.edu/pub/den/deming_map.htm) used in statistical process control bear a felicitous correspondence to the iterative debugging cycles used by computer programmers.

Our hospital has an amnesty policy that prohibits disciplinary action against physicians, nurses, pharmacists, and other health-care workers who voluntarily report medication errors. Our hospital also has a program to identify drug therapy flaws, including hazards and failures, medication errors, and ADEs. ADE detection methods included concurrent review of hospital records by nurse quality managers with respect to resuscitations, unplanned intensive care unit transfers, and nonelective endotracheal intubation or noninvasive ventilation, perievent discontinuation of drugs, unplanned use of antidotes, toxicology laboratory reports, and ADE voicemail hotline reports. An ADE was defined as "an injury related to the medical use of a drug."[3]

We assessed ADE causality using the Naranjo scale,[50] a validated instrument having a high interrater reliability[51] and objective signs such as pulse oximetry, resuscitative use of naloxone, and respiratory arrest. A Naranjo score >4 was considered to be above the causality threshold. We graded the adverse event as mild, moderate, severe, or fatal. Events were considered severe if patients had an opioid-associated ADE requiring life-saving intervention, such as unplanned intensive care unit transfer, unplanned use of resuscitative dose of naloxone (≥0.4 mg), nonelective endotracheal intubation, or noninvasive ventilation. Supportive data included low cutaneous hemoglobin O_2 saturation, documentation of unarousability, favorable response to naloxone or discontinuation of opioids, and clinician assessment.

Nurse quality managers, clinical pharmacists, and physician abstractor/evaluators were trained to abstract ADE data. Competence was maintained by periodic refresher training and cross-validation by expert reviewers. We periodically calculated Cohen's κ scores for causality and severity assessments, and confirmed a high inter-rater reliability for these assessments among evaluators in our hospital as earlier described.[52] We used the MIDAS+ medical information software (Midas+ Care Management System, Version 6.1r5; ACS Healthcare Solutions/Midas+, Tucson, AZ) to collate hospital ADEs, identify hazard and error patterns, and track progress. An abstractor/evaluator who was blinded to information regarding routine ADE evaluation conducted a separate abstraction and evaluation for all 496 patients who received either POPA or routine PCA after major orthopedic hip or knee surgery from January 1998 to December 2002.

Statistical analysis

Statistical process control analysis: Severe/fatal opioid-associated ADEs were collated by month and analyzed with a u-type process control chart using Statview 5.0 (SAS Institute, Cary, NC). Exact *P* values were calculated by resampling with a standard Poisson model using Mathematica 5.2 (Wolfram Research, Champaign, IL).

Analysis of diffusion of innovation: We used Mathematica 5.2 to calculate POPA's hospitalwide diffusion half-life by optimal fit of the logistic growth equation to quarterly POPA cartridge purchases as obtained from hospital pharmacy purchase data (**Figure 2**).[53,54] In order to facilitate an approximate comparison of opioid prescription trends, we express the amounts of morphine, meperidine, and hydromorphone as grams of FE using the equivalency relations: fentanyl 100 μg = morphine 10 mg = meperidine 80 mg = hydromorphone 1.3 mg.

Orthopedic surgery cohort analysis: Exact *P* values for the univariate analyses were calculated using resampling or Fisher's exact test. The multivariate nonlinear model for predicting which of the patients would have a severe or fatal opioid-associated ADE was calculated by conducting hierarchically optimal classification tree analysis.[55] The type I error rate for the overall model was ensured at $P < 0.05$ using a sequentially rejective Sidak Bonferroni–type procedure for multiple comparisons. The univariate analyses and classification tree analysis were carried out using Optimal Data Analysis[56] (**Table 3**).

ACKNOWLEDGMENTS

This study was funded by Food and Drug Administration grant FD-R-000887, Caterpillar and OSF Saint Francis Medical Center. S.M.B. was supported in part by an American Heart Association grant and by American Cancer Society grant RS-GHP-05-215-01-CPPB. The OSF Saint Francis Medical Center Pharmacy and Therapeutics Committee provided oversight for the POPA drug therapy improvement project. The Peoria Community Institutional Review Board approved the chart review and data analysis necessary for evaluation of the POPA project. Caterpillar manufactured the mechanical visual analog scales to our specifications. We thank Dr Tim Miller for his support.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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