Final Progress Report

Reducing Adverse Drug Events from Anticoagulants, Diabetes Agents and Opioids in Primary Care

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Project Dates: 9/30/2014-9/29/2018

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Agency Support: This project was supported by grant number R18HS023454 from the Agency for Healthcare Research and Quality. The content is solely the responsibility of the authors and does not necessarily represent the official views of the Agency for Healthcare Research and Quality.

Grant Award Number: 5R18HS023454-03 REVISED

1. STRUCTURED ABSTRACT

Purpose and Scope: Reducing harm from adverse drug events (ADEs) is a national patient safety priority. High-priority medications (HPM), defined as anticoagulants, diabetes agents, and opioids, have been associated with clinically significant and preventable ADEs. The project's goals were to develop ADE clinical quality measures (CQMs) for HPM and test the impact of a community-engaged action (CEA) research approach on practice performance on ADE CQMs. *Methods:* Previously published ADE risk factors were augmented with findings from a literature review to derive CQMs. A provider survey assessed agreement with CQMs. All practices received performance reports on CQMs throughout the 18-month group-randomized trial. Intervention group practices invited patients on HPM to serve as advisors during project site visits. *Results:* The measure development process resulted in nine CQMs. The 20 participating practices represented 109 clinicians from 17 US states. In total, 77 patient advisors participated in intervention site visits. Intervention practices improved on two anticoagulant CQMs compared with control practices; control group practices improved on Avoiding Potential Overtreatment of Diabetes and Proportion of Adult Patients with an Opioid Prescription. Control and intervention practices improved on Avoiding CNS Depressants in Patients on Long-term Opioids. There was no difference in the adjusted change between groups in three other CQMs. For a project in which all practices contributed to measure development and received reports, site visits with patient advisors did not result in additional improvements. A broad focus on HPMs and selected patient advisors may have diluted the power of the intervention.

Key Words: medication errors, patient safety, practice-based research network

2. PURPOSE

The objectives of this study were to:

1) Clarify risk factors for ADEs from high-priority medications through a literature review and translate them into a working set of clinical quality measures that can be implemented in primary care.
2) Use a community-engaged action (CEA) research approach to test the impact of a refined set of preventive strategies for ADEs on practice performance on ADE clinical quality measures.

3. SCOPE

Background

Improving safe medication use by decreasing adverse drug events (ADEs) is a fundamental priority for transforming the US healthcare system. ADEs are defined as "injuries resulting from medical intervention related to a drug."[1] Preventable or ameliorable ADEs are those that could have been avoided or mitigated in duration or severity by heightened monitoring or more optimal care management.[2,3] The "National Action Plan for ADE Prevention" (NAP) highlights the need for focused attention on the surveillance, prevention, and research of measurable, preventable or ameliorable ADEs from high-priority medications (HPM).[4] Due to the frequency of clinically significant and preventable ADEs across inpatient and outpatient settings, anticoagulants, diabetes agents, and opioids have been identified as HPM.[5-7] The NAP has identified dosing, interactions, and inadequate patient education as risk factors for prescribing-related ADEs and use of aggressive disease management targets and lack of systematic follow-up approaches as monitoring-related risk factors. However, the evidence base for *how* to effectively manage ADE risk factors beyond research[8,9] or hospital settings[10-14] remains underdeveloped. Additionally, there are limited examples of engaging patients in the safety improvement process.[15-17]

Context

In prior AHRQ-funded medication safety projects,[18-20] the PPRNet research team established a broad set of primary care-relevant prescribing and monitoring error quality measures and a practice-based improvement model. This project was designed in response to the NAP[4] and calls for engaging patients and their caregivers in advancing the safety evidence base. Volunteer practices were members of a national primary care practice-based research network, expressed interest and a commitment to improving safe medication use, and agreed to invite patient and caregivers to participate as advisors to the practice.

Participants

Twenty-nine PPRNet practices volunteered to participate during the first quarter of the project. PPRNet was an AHRQ Center for Primary Care Research and Learning at the Medical University of South Carolina, and member practices from across the United States regularly pooled electronic health record (EHR) data for the purposes of quality improvement and translational research. One practice, due to their experience with local advocacy for safe opioid prescribing, opted to participate as an advisor to the research team. Three practices did not respond to requests confirming their participation prior to randomization, and two practices dropped out because they were not able to submit EHR data to PPRNet. PPRNet membership required that practices utilize EHR technology with the ability to batch-export Summary of Care documents (core objective # 15) in cCDA format, as prescribed in the Meaningful Use Stage 2 Final Rule.

Twenty-three PPRNet practices were randomized, using a modified constrained randomization process: 12 into an intervention group, and 11 into a control group. Prior to the first intervention site visit, two practices dropped out due to inability to adhere to study protocol, and one practice dropped out due to closing their practice. Nine intervention group practices hosted two site visits, and eight hosted a total of three visits. A total of 77 patient advisors participated in initial intervention site visits. The 20 practices included in final analyses represent 109 physicians and advance practice providers (median 3, range 1-24 providers per practice) from 17 US states.

4. METHODS

Aim 1) Clarify risk factors for ADEs from high-priority medications through a literature review and translate them into a working set of clinical quality measures that can be implemented in primary care.

ADE risk factors were identified from the “National Action Plan” and augmented with findings from a literature review to derive CQMs that were supplemented by existing or proposed “EHR Meaningful Use” CQMs. Because the preliminary set of ADE CQMs was comprehensive but shorter than projected, the provider survey approach was adapted to assess agreement with CQMs and open comments to justify disagreements and suggest modifications. The survey was delivered via REDCap™ to project liaisons with a request to share with all providers; two rounds of email reminders went to nonresponders.

Aim 2) Use a community-engaged action (CEA) research approach to test the impact of a refined set of preventive strategies for ADEs on practice performance on ADE clinical quality measures.

The 18-month intervention period began on January 1, 2016. Practices in both study groups received performance reports on ADE CQMs throughout the 18-month intervention. Practices were encouraged to submit data monthly, with PPRNet staff prompting for quarterly data submissions.

The community-engaged research approach for this project added patient or caregiver advisors on HPM to established PPRNet-TRIP methodology.[21] Each intervention practice hosted an introductory project site visit designed to educate participants on preventable ADEs from HPM, present the set of proposed ADE CQMs, and review practice performance on the CQMs. Agendas for follow-up site visits were customized to the practice's goals and generally included relevant new evidence on HPM ADEs, practice performance on ADE CQMs, and follow-up and planning practice strategies to improve performance on ADE CQMs. Early lessons from across the intervention group were also shared during the second and third site visits, spreading best practices for implementing specific safety strategies.

The primary outcome of the project was practice performance on ADE CQMs, listed in Table 1. Each CQM was calculated at the patient level, with patients either satisfying criteria or not. CQMs, for the purpose of standardization, were expressed as avoidance of ADE risk factors. For example, in "Avoiding High-dose Opioid Therapy," the criteria were defined as current opioid prescription(s) at a daily dose of less than or equal to 100 mg of morphine equivalent doses among the denominator of adult patients with an active prescription for any opioid (excluding patients with documentation of palliative or end-of-life care). Qualitative content analyses were applied to intervention site visit field notes; Drs. Nemeth and Wessell reviewed input from patient advisors on strategies to reduce harm and identified key themes across practices.

Table 1: Adverse Drug Event Clinical Quality Measures

Anticoagulants
INR in 56-day Interval for Patients on Warfarin
Repeat INR Monitoring for Patients on Warfarin After Starting an Anti-infective Medication
Appropriate Dosing of NOACs in Patients with Renal Dysfunction
Annual Renal Function Monitoring for NOACs
Diabetes agents
Avoiding Potential Overtreatment of Diabetes: Most Recent A1C > 7% for High-risk Patients on Insulin or Sulfonylureas • High risk: age > 75 years, serum creatinine > 2 mg/dL, dementia, or age > 65 with diabetic retinopathy, nephropathy, substance dependence, limited life expectancy
Opioids
Avoiding High-dose Opioid Therapy (Total daily doses of > 100 mg morphine equivalent dose)
Avoiding CNS Depressants (benzodiazepines, skeletal muscle relaxants, or sedative hypnotics) in Patients on Long-term Opioids
Toxicology Screening in Patients on Long-term Opioids
Alcohol and/or Other Substance Abuse Screening in Patients on Long-term Opioids

Data Sources

Change in practice performance on ADE CQMs was analyzed using data from routine practice EHR data extracts. Qualitative data sources included field notes from intervention site visits.

Measures

The ADE CQMs are summarized in Table 1. These CQMs were incorporated into PPRNet audit and feedback reports on performance at the practice and provider levels, including patient registries. In response to feedback during initial site visits, an additional measure that reflected overall opioid prescribing was added to reports starting in May 2016.

Limitations

Dosing CQMs (for new oral anticoagulants and opioids) depended on complete dosing data in EHR cCDA extracts. The selection of patient and caregiver advisors was limited by including patients on any HPM and those that were able to attend project site visits, which were held during traditional work hours. The project timeline overlapped with growing attention and public health and prescribing-based responses to the opioid overdose epidemic; new national prescribing guidelines[22] were disseminated during the last 8 months of the project. The evaluation of how recommended safety strategies were adopted in practice was limited to intervention group practices. Practices were members of a practice-based research network and volunteered to participate in a project designed to reduce HPM ADEs, which may limit the generalizability of our findings to other primary care practices or settings.

5. RESULTS

Principal Findings

We received 51 total responses from 24 practices (range 1-6 providers; missing practice identifier in seven responses) to the ADE CQM development survey, resulting in a practice response rate of 83% (n = 29 practices). Overall, there was moderate to high agreement with preliminary CQMs. The working set of CQMs, as shown in Table 1, was incorporated into reports and disseminated to all participating practices during the 18-month group-randomized trial.

Results on practice performance the ADE CQMs from repeated measures analyses, using generalized linear mixed models for longitudinal data and adjusted for practice-level clustering, are shown in Table 2. Results are not shown for three ADE CQMs due to small sample sizes (INR in 3-7 days for Patients on Warfarin and Interacting Anti-infectives) and incomplete EHR data (Toxicology Screening in Patients on Long-term Opioids and Alcohol and/or Other Drug Use Screening in Patients on Long-term Opioids).

For the seven measures analyzed in Table 2, there was no difference in the adjusted change between groups in three measures. Intervention practices improved on two anticoagulant measures compared with control practices; control group practices improved on Avoiding Potential Overtreatment of Diabetes and Proportion of Adult Patients with an Opioid Prescription measures. Both control and intervention practices improved on the Avoiding CNS Depressants in Patients on Long-term Opioids CQM.

Table 2: Results - Practice Performance and Adjusted Change on Adverse Drug Event Clinical Quality Measures by Group

	Control Practices (n = 11)			Intervention Practices (n = 9)		
ADE Clinical Quality Measure	**Baseline (n) [Practice Range]**	**Month 18 (n) [Practice Range]**	**Adjusted Change**	**Baseline (n) [Practice Range]**	**Month 18 (n) [Practice Range]**	**Adjusted Change**
Anticoagulants						
INR in 56-day Interval for Patients on Warfarin	67.2% (629)	60.5% (567)	-14.0%	67.9% (374)	66.6% (305)	-1.3%*
Appropriate Dosing of NOACs in Patients with Renal Dysfunction	95.8% (312)	97.2% (362)	1.9%	96.0% (199)	97.3% (335)	1.9%
Annual Renal Function Monitoring for NOACs	91.0% (343) [63-100%]	85.2% (426) [39-95%]	-7.2%	87.7% (228) [78-100%]	92.0% (364) [67-100%]	0.6%*
Diabetes Agents						
Avoiding Potential Overtreatment of Diabetes[#]	90.6% (1650) [69-98%]	92.0% (1715) [77-100%]	1.3%*	93.1% (1244) [87-100%]	92.5% (1353) [90-100%]	-2.0%
Opioids						
Avoiding High-dose Opioid Therapy[-]	94.4% (1901) [75-97%]	94.2% (1557) [83-95%]	0.6%	92.2% (1741) [82-98%]	91.7% (1191) [83-97%]	0.5%
Avoiding CNS Depressants in Patients on Long-term Opioids[~]	62.5% (2585) [54-93%]	65.7% (2160) [55-83%]	6.5%	59.5% (1685) [39-90%]	63% (1282) [42-90%]	5.8%
Proportion of Adult Patients with an Opioid Prescription[~]	11% (28,522) [2-21%]	10% (26,070) [2-21%]	-0.5%*	12.2% (17,036) [4-18%]	10.2% (14,723) [5-18%]	-0.2%

Potential overtreatment defined as A1C < 7% and current insulin or sulfonylurea prescription in eligible adult patients with A1C recorded in the past year and any high-risk condition (age >= 75 years; serum creatinine >=2 mg/dL; diagnosis of dementia; age >= 65 with diabetic retinopathy; age >= 65 with diabetic nephropathy; age >=65 with limited life expectancy or on palliative care; age >= 65 with alcohol or drug dependence; * $p<0.0001$; - In patients on opioids with complete dosing data for calculation of morphine equivalent doses; two control and one intervention practice with incomplete dosing data; ~ Active patients with at least one medication in PPRNet CQMs (e.g., antidepressants, antihypertensives, nonsteroidal anti-inflammatory drugs, statins).

Qualitative Findings

Based on direct observation and notes from each of the initial intervention site visits, four themes indicated that patients value 1) trust between patient and provider, 2) education focused on individual risk, 3) regular laboratory monitoring of HPM, and 4) consistent communication from practice clinicians and staff. These perspectives centered on personal relationship and risk for harm, validated practice approaches to monitoring and communicating risk, and offered support for new approaches.

Exploratory Findings

In a follow up to results on the Opioid CQMs in this project, the US opioid overdose epidemic,[23] opioid prescribing patterns,[24] and recommendations for naloxone co-prescription as a strategy to reduce risk from chronic opioids,[22,25,26] we evaluated naloxone prescribing in a subset of participating practices. These practices volunteered to participate in a project proposal that we submitted to the National Institute on Drug Abuse. Data from nine practices (all independent primary care practices with a median of three providers from eight US states), in Table 3, show variations across practices in overall opioid prescribing, the proportion of patients on higher daily doses (over 50 MME per day[22]), and the proportion of patients taking both chronic opioids and CNS depressants. Most notably, a total of only five patients had an active naloxone co-prescription.

Table 3: Preliminary Opioid and Naloxone Prescribing Data (as of June 30, 2017

Practice	Patients with opioid rx (%) (n eligible patients*)	Patients on > 50 MME# (%) (n eligible patients~)	Patients on chronic opioids and CNS depressants• (%) (n eligible patients^)	Patients on chronic opioids and naloxone (%) (n eligible patients^)
A	3.3 (1717)	24.6 (57)	16.7 (48)	2.1 (48)
B	5.5 (5018)	unavailable dosing data	24.6 (167)	0 (167)
C	6.5 (1274)	4.8 (83)	18.7 (75)	1.3 (75)
D	6.5 (1146)	17.6 (74)	38.6 (70)	0 (70)
E	7.5 (348)	26.9 (26)	45.5 (22)	0 (22)
F	8.8 (1835)	8.6 (162)	27.8 (126)	0 (126)
G	13.2 (4821)	9.9 (638)	34.9 (550)	0 (550)
H	18.3 (3396)	27.5 (622)	43.9 (531)	0.2 (531)
I	19 (2076)	16.8 (392)	44.8 (357)	0.56 (357)

* Active adult patients with at least one medication in PPRNet clinical quality measures (e.g., antidepressants, antihypertensives, nonsteroidal anti-inflammatory drugs, statins); # Morphine milligram equivalent per day, calculated with available dosing data and conversions defined in [27];
~ Active adult patients with opioid prescription; • Central nervous system depressants: benzodiazepines, muscle relaxants, sedative hypnotics; ^ Active adult patients with opioid prescription for at least 90 days.

Discussion

Practice site visits with patient advisors, for a project in which all practices contributed to measure development and received regular reports, did not result in additional improvements in a set of ADE CQMs. A broad focus on multiple HPMs and selected patient advisors may have diluted the power of the intervention to impact individual CQMs. Future work should focus on reducing variability across opioid CQMs and examine alternative roles for patient advisors in primary care.

Implications

There are implications of these findings for the evolving patient safety evidence base. As outlined in the National Action Plan, CQMs for new oral anticoagulants are relevant for the growing population of patients on these medications. The “Avoiding Potential Overtreatment of Diabetes” measure could strengthen diabetes measure sets by adding a measure of potential harm to existing quality-centric measures. Practice-level variability in opioid and CNS depressant prescribing is consistent with national trends and underscores the need for further improvement. Naloxone co-prescribing recommendations have not yet been broadly adopted.

Selected ADE CQMs from this project were incorporated into the PPRNet 2017 CMS-recognized Qualified Clinical Data Registry measure set. CMS reviewers rejected the “Avoiding Potential Overtreatment of Diabetes” CQM, because it was viewed as controversial, and the “Avoiding Use of High-dose Opioid Therapy” CQM, due to the high-dose therapy definition.

Through existing partnerships of project investigators and the new PPRNet Foundation (www.PPRNet.org), we have also disseminated the ADE CQMs to other interested groups, including the DARTNet Component Patient Safety Organization and Clinigence® Qualified Clinical Data Registry Practices (including former members of PPRNet and new users) who receive reports from Clinigence® benefit from near-real-time feedback on the ADE CQMs.

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