REVIEW

Potential value of electronic prescribing in health economic and outcomes research

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Abstract: Improving access and quality while reducing expenditures in the United States health system is expected to be a priority for many years. The use of health information technology (HIT), including electronic prescribing (eRx), is an important initiative in efforts aimed at improving safety and outcomes, increasing quality, and decreasing costs. Data from eRx has been used in studies that document reductions in medication errors, adverse drug events, and pharmacy order-processing time. Evaluating programs and initiatives intended to improve health care can be facilitated through the use of HIT and eRx. eRx data can be used to conduct research to answer questions about the outcomes of health care products, services, and new clinical initiatives with the goal of providing guidance for clinicians and policy makers. Given the recent explosive growth of eRx in the United States, the purpose of this manuscript is to assess the value and suggest enhanced uses and applications of eRx to facilitate the role of the practitioner in contributing to health economics and outcomes research.

Keywords: electronic prescribing, outcomes research, health information technology

Background on electronic prescribing

At its inception, electronic prescribing (eRx) was seen as a quality improvement tool and was defined as "the prescriber's ability to electronically send an accurate, error-free, and understandable prescription directly to a pharmacy from the point-of-care".[1] A more recent and comprehensive definition of eRx that we use throughout this article is the transmission, using electronic media, of prescription or prescription-related information between a prescriber, dispenser, pharmacy benefit manager, or health plan, either directly or through an intermediary, including an eRx network.[2]

A systematic review of the effects of computerization on doctors' performance from 1980 to 1997 found that eRx was the most commonly used feature of general practice computing and that computing systems could increase preventive health services, improve medication efficiency (generic utilization and cost), and decrease physician/staff time.[3] Since 1997 (the end of the study period), the use of eRx has increased dramatically, particularly following the creations of the RxHub and the SureScripts networks, which have since merged. Despite its rapid growth, widespread use of eRx is not yet a reality, with approximately 26% of office-based United States (US) physicians using eRx and only 30% of them taking advantage of formulary information, according to the 2009 annual SureScripts report.[4]

The eHealth Initiative and the Center for Improving Medication Management, both nonprofit organizations chaired by national leaders in health care, published a joint report in June 2008, which provides a basis for understanding eRx as a type of health

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information technology (HIT).[5] Computerized physician order entry (CPOE), often seen in the literature in reference to hospital systems, usually includes eRx. In fact, CPOE originated in most inpatient settings primarily to manage cost and quality in the physician–pharmacy interaction.

ERx capabilities can exist within simple standalone systems or integrated within electronic health record (EHR) or electronic medical record (EMR) systems. These systems can be programmed to offer clinical and/or formulary decision support at the point of prescribing. Depending on the capabilities of the eRx system, the physician can access patients' medication histories, including drugs that have been previously prescribed by other doctors, and medication allergies. If the eRx system is imbedded within an EHR system, there is greater availability of information such as medical history, laboratory data and past hospitalizations. As of 2010, certain standalone eRx systems are starting to include problems/diagnoses and laboratory results, without attempting to be an EMR.

An additional electronic database of importance to health outcomes research is being generated through medication therapy management services (MTMS) provided by pharmacists within the practice of pharmaceutical care.[6–8] MTMS documentation systems (eg, Assurance, HealthMapRx, and others) track the patient's progress toward achieving goals of therapy including the management and resolution of drug therapy problems.[9,10] The Office of the National Coordinator for Health Information Technology (ONC) is reviewing a "meaningful use" petition for a certified pharmacy EHR separate and distinct from pharmacy medication dispensing systems.[11] Initiatives for conducting health economics and outcomes research can be expected to benefit from the integrated use of eRx, EHR, and patient outcomes information contained in MTMS documentation systems. Along these lines of "meaningful use", eRx software should be certified by ONC-recognized and newly created IT certifying organizations such as the Certifying Commission for Health Information Technology (CCHIT).[12] Standalone eRx systems have already started the CCHIT certification process in the 2009–2010 timeframe.

eRx has many benefits over traditional prescribing for prescribers, pharmacies, patients, and payers (Table 1).[13] ERx eliminates the ambiguities inherent in interpreting handwritten prescriptions.[12,14,15] eRx has potential to add value to patient care and decrease costs, ideas supported by both private and public sectors.[16] In June 2009, the American Medical Association (AMA) announced it would sponsor an innovative "Cloud Computing" platform. Most importantly, its first main clinical feature was standalone eRx. Plans to integrate other clinical functions through modular components to emulate many EMRs have already been realized.

Some pay-for-performance (PFP) programs provide bonuses to physicians who adopt eRx or EMR[17] and Title XIII of the American Recovery and Reinvestment Act (ARRA) deals with encouraging physicians to use more HIT which includes incentives for eRx, mainly through Medicare and Medicaid. The federal reimbursements amount to between $44–64,000 earned over a 5-year period starting in January 2011. In addition, the patient-centered medical/health home initiative advocates for increased payments to health teams for achieving clinical benchmarks in the patients they serve.[18]

But there is added value from eRx beyond monetary gains and fulfilling requirements. The use of eRx with appropriate security and selectively deidentified data allows practitioners to contribute to research, improve performance and gather insight into aspects which may become publicly reported. ERx data can be used to answer research questions about health and economic outcomes of medical care. An important step in being able to use this data source is to determine the accuracy and reliability of the information.

Evaluation of eRx data

Eguale et al looked at the accuracy of eRx in documenting medication discontinuation or dosing changes by comparison with physician facilitated medical chart review.[19] They determined that eRx was reconciled with paper records 80%–95% of the time and concluded that eRx is a new method for augmenting pharmacosurveillance.

Despite the accuracy of eRx in evaluating certain parameters, there are also documented risks for using eRx, which may or may not relate to the systems design. Technology may not do what it has been intended to do and may lead to unintended consequences such as patient harm or misused resources.[20] There are few randomized, prospective controlled trials comparing the adverse effects of eRx systems. Typical study designs evaluate some aspect pre- and post-implementation of the eRx system. Since implementing a system usually means a major change in workflow; it may be hard to confirm if the outcome is due to the eRx system or the workflow change. Also, it is difficult to determine the unit of analysis in some studies – is it the hospital system, the single health care provider, or an isolated number of patients? Observational methods are more common and can provide real-world approximations of the usefulness of eRx systems.

One of the problems noted with eRx is that clinicians may choose the wrong medication. There are patient safety initiatives occurring to correct this error such as the inclusion of *International Classification of Diseases*, *9th Revision*,

Table 1 Benefits of electronic prescribing (eRx)[13]

Insurers	Prescribers	Pharmacies	Patients
• Improved formulary compliance • Reduction of medication errors • Identification of patient nonadherence • Reduction of overall health care costs • Provides formulary support (lessens burden for prior authorization/step edits for prescribers to contact insurance); Medicare Part D formulary must be loaded to eRx software • Reduce health care costs – encourages generics, lower cost options	• Display of alternative medications with economic benefit • Reduction of medication errors (eg, drug–drug, drug allergy, drug duplication) • Reduction of work-flow interruptions (calls and faxes from pharmacies, patients, and payers) • Improvement of patient adherence • Financial incentives for adopting eRx systems – Physician reimbursement programs • Can monitor patient adherence • Clinical decision support software can be built according to needs of practice, including on-screen prompts for drug-specific dosage information • Creates complete medication history – prescriber able to see prescriptions ordered by other prescribers • Practice evaluation: adherence to clinical guidelines, adaptation to initiatives, documenting outcomes • Maintains vital patient-specific information • May reduce fraud and abuse especially in the "doctor shopper" category for controlled substances	• Reduction of dispensing errors related to illegible handwriting and look-alike/sound alike drugs • Reduction of work-flow interruptions (calls to prescribers, patients, payers) • Enhanced time for patient counseling • Can monitor patient adherence • Eliminates "falsified" written prescriptions • May reduce fraud and abuse • Streamlines and reduces faxes (duplicates, missing) sent by pharmacy to prescriber for refills, expedites refills	• Patient convenience: Patient may pick up prescription from pharmacy without dropping off prescription • Reduction of medication errors • Reduce health care costs – encourages generics, lower cost options

Clinical Modification (ICD-9-CM) codes on electronic prescriptions, mandatory patient counseling at the time of dispensing a new prescription, and the use of MTMS in patient-centered medical/health home designed to help patients achieve goals of therapy.

Value of eRx data in outcomes studies

The use of administrative claims databases is common in health outcomes research and quality of care assessments.[21] Medical claims data contain ICD-9-CM codes to identify diagnoses whereas pharmacy claims provide information about prescription drug usage. Although claims are intended for billing purposes, researchers have been able to examine them from a population standpoint to evaluate care, gather statistical data, and look at possible interventions more efficiently than performing traditional chart reviews. Even though claims data in research can provide a great deal of information on diagnoses, procedures, and medication use, this type of data has also been criticized for capturing limited information which may not fully reflect the patient's condition.[22]

The use of eRx data either from standalone systems or within EMR systems provides opportunities beyond claims data. For example, pharmacy claims data has been frequently used to evaluate persistence or adherence with medication therapy. The use of claims data can determine the length of time a patient possessed a specific medication. However, it fails to differentiate whether non persistence is prescriber or patient initiated. In addition, pharmacy claims data fail to identify those patients who have been prescribed therapy, but never filled their prescriptions (ie, first-fill failure). Due to the fact that few non prescription medications are covered by insurers, pharmacy claims data are only sparsely populated with over-the-counter drug and herbal medicine data. Conducting research with eRx data provides an efficient way to determine whether the patient did not obtain the prescribed or intended medication, sometimes referred to as first-fill failure. If a prescriber e-prescribes hydrochlorothiazide (HCTZ) for her patient, this would allow for the capture of the electronically prescribed HCTZ. A matching pharmacy claim for this patient for HCTZ would confirm that the patient obtained the medication. However, if the patient never picked up the prescription, there would be no matching pharmacy claim. The use of eRx data would identify that this patient failed to pick up the intended medication. In previous research studies where only pharmacy claims data were examined, this patient would not have been identified. Not only was this research question previously unanswerable in claims data, but it required time-consuming

and very expensive manual chart-review where such data was sometimes difficult to locate.

Even though eRx systems were not originally developed for research, investigators have conducted studies using eRx information to understand medication adherence, compare utilization and effectiveness of therapies, evaluate the effects on medication errors, and describe the impact on physician prescribing and clinical outcomes (Table 2).

Within a practice or health system, data from eRx can be used to document quality care and to evaluate the impact of clinical initiatives on patient care outcomes. The point-of-care feedback that eRx systems can offer the practitioner impacts appropriateness of prescribing, compliance to formulary, and medication adherence. This provides an electronic dataset for studying changes in outcomes based on various types of clinical decision support (CDS).

Published studies which have used eRx data within outcomes research can be found in Table 3.[15,19,23–44] The research addresses evidence-based medicine and guidelines, medication adherence, comparative effectiveness, economic evaluations, and medication errors. These studies provide a basis for examining the value of eRx to the practitioner for clinical purposes and as a component of the practitioner's contribution to an emerging body of research around real world drug utilization and surveillance. Study highlights are presented to show the practitioner the plethora of information that can be collected and studied using eRx data (Table 3).

Table 2 Opportunities for using electronic prescribing in outcomes research

- Pharmacosurveillance/adverse drug events
- Public health (surveillance/syndromic surveillance)
- Evidence-based medicine (clinical practice guidelines)
- Pharmacoepidemiology
- Joint Commission on Accreditation of Healthcare Organizations (JCAHO)
- Pay-for-performance programs
- Comparative effectiveness research
- Medication errors
- Drug interactions
- Evaluation of clinical decision support:
  - Allergy warnings
  - Contraindicated drugs (relative or absolute)
- Medication adherence
- Quality improvement initiatives
- Formulary compliance
- Pharmacoeconomics
- Added tools for research in fraud and abuse, particularly in controlled substances [when approved by the Drug Enforcement Administration]

Future directions

Studies that focus on the quality, efficiency and cost of care are important to clinicians, institutions, and the entire US health care system. Several factors will impact the future use of eRx data in outcomes research.

Infrastructure development/support

Large amounts of federal funds have been allocated to boost the use of health care technology, including grants for outcomes research studies. Under the Health Information Technology for Economic and Clinical Health (HITECH) Act, as part of the $19.2 billion program promoting the adoption and use of EHRs, the government is providing over $300 million to regional HIT efforts to create the infrastructure necessary to promote electronic exchange and the use of health information.

One area of concern among experts in the future of health outcomes and economics evaluation is that the Health Insurance Portability and Accountability Act (HIPAA) hinders important medical research studies.[45] The management and use of eRx data offers both new solutions to privacy as well as new potentially problematic areas. While prescriber level data aimed at marketing is not an appropriate use, quality improvement and research initiatives using aggregated eRx data are. Many clinicians require their patients to sign waivers to allow access to their medication information for deidentified analyses. The use of aggregated and deidentified eRx data as a secondary data source can be classified by institutional review boards (IRBs) as having a low level of risk to subjects falling within the exempt review category of research.[46] The use of this data involves no more than a minimal risk defined as, "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations of tests." Many IRBs allow for a waiver of patient consent.

Additionally, eRx and EMR systems can actually be a way for health care professionals to comply with HIPAA and decrease the amount of paperwork. In Europe, the United Kingdom, Denmark, and The Netherlands, EMR systems can perform full audit trails for access, and patients are entitled to know who has looked at their information and what information each person had viewed. Patients are ultimately given the choice to opt in, opt in with restrictions, or opt out.[47] If patients have access to their eRx and EHR in the US, they can be given this choice as well.

A committee from the Institute of Medicine (IOM) calls on Congress to authorize a totally different approach to safeguarding personal health data in research regardless of who supports or performs the research. Implementing recommendations of the IOM can be expected to facilitate scientific discovery and medical innovation necessary to enhance the quality of the public's health.

Many if not all the federal subsidies included under the ARRA and HITECH laws to assist in the purchase or reimbursement for clinical information technology targeted to physicians, hospitals, and health care providers will be contingent on the demonstration of "meaningful use" as defined by the ONC under The US Department of Health and Human Services. This specification requires that the applications must demonstrate not only improved outcomes, but lowered costs or avoidance of substantial rises in costs. The most commonly cited example of "meaningful use" in the eyes of the federal regulators as well as many think tanks is eRx.[48]

Research utilizing eRx data may be much simpler as systems can talk to each other. Many vendors are already working on system certification and data interoperability standards that support government reporting as well as privacy and security requirements. The purpose is to create software that uses EHR data within the context of clinician's workflow to simplify the use of data for secondary uses, thereby reducing the need for re-entering data.

Increased research power is possible with eRx because it allows for aggregation of data from different sources. Large patient registries for evaluating patient outcomes will be created, such as the Distributed Ambulatory Research in Therapeutics Network (DARTNet), a network of some 500 clinicians using EMR designed to compare effectiveness of prescription medications and medical devices.[49] The DARTNet research team can query the database to obtain information about care and outcomes for hundreds of thousands of patients. In addition, the Agency for Healthcare Research and Quality has already published a user guide providing key information on developing, operating and evaluating patient registries, electronically available at www.ahrq.gov.[50] With increased pervasive use of eRx by hospitals, institutions, and physician offices, more opportunities for outcomes research that allow real-world evaluations of care emerge. As each patient's record is added to an ever growing database of evidence, this aggregation of information is extremely powerful for answering questions that could not be answered previously.

Pharmacoeconomic research

The considerable recent emphasis from all stakeholders in health care, especially in light of the federal government's attempts to reform the system, point to importance of cost efficacy in future research outcomes. The addition of eRx clinical data to the research outcomes community makes studies of both new and older drugs that focus on reduced costs much easier and in fact compelling. For example, a new drug that is shown to be noninferior to an older drug, but demonstrates significantly less hospitalizations, adverse drug events (ADEs), and/or less expensive testing to monitor potential ADEs would have a major appeal. Such drugs have already been introduced to the market with those characteristics in mind when the applications for approval were submitted to the US Food and Drug Administration (FDA).

Population health management

Randomized controlled clinical trials (RCTs) are the basis for new therapies to be evaluated for approval by the FDA (safety and efficacy) as well as serving as the groundwork to make evidence-based treatment decisions (comparative effectiveness). In order to more fully assess drug safety, we rely on epidemiology or post-marketing trials to provide additional insight. Regulatory agencies such as the FDA and the Drug Enforcement Administration can take advantage of the data found in eRx systems for pharmacosurveillance purposes. Current pharmacosurveillance methods are retrospective and do not provide timely information on drug safety and effectiveness. Through eRx, real-time information can improve medication error or drug adverse event reporting if an automated surveillance system is set up. Regulatory agencies will no longer need to rely only on clinician or institutional directed reporting.

Research based on real-world data from eRx can provide supplemental evidence to RCT in population health management. While RCTs can address differences in drug efficacy in a controlled environment, there is often little incentive for pharmaceutical manufacturers to conduct RCTs with active comparators. There is a lack of literature on the relative effectiveness of therapies for a specific condition, especially agents within the same pharmacologic class. Using real-world data from eRx will enable more information on the comparative effectiveness and benefit versus risk profiles of medicines and treatments, especially for population-based decisions such as medication formularies.

Clinical decisions are often made by extrapolating evidence from clinical trials where the patient sample demographics do not match the clinician's patient. If practitioners have access

Table 3 Published studies which have used eRx data within outcomes research

Reference	Research area	Practice setting	Study objective	Study design	Data elements	Outcome measures	Results
Astrand[23]	Medication errors	Outpatient	To assess the quality of ePrescriptions by comparing the proportions of ePrescriptions and non-electronic prescriptions necessitating a clarification contact (correction, completion, or change) with the prescriber at the time of dispensing	Prospective, observation	eRx/traditional Rx sent to mail-order pharmacy (observers shadowed pharmacies, did not extract data electronically)	Numbers and frequencies of prescriptions necessitating a clarification contact, causes of clarification contacts, time and results of interventions	Clarification contacts made for 2.0% (147/7532) of new ePrescriptions and 1.2% (79/6833) of new non-electronic prescriptions, RR of 1.7 (95% CI: 1.3–2.2) for new ePrescriptions versus new non-electronic prescriptions. The increased RR was mainly due to 'Dosage and directions for use', which had an RR of 7.6 (95% CI: 2.8–20.4) when compared to other clarification contacts.
Belperio[24]	Clinical	Outpatient	To assess the concordance with VHA guidelines for use of atazanavir, darunavir, enfuvirtide, and tipranavir, and describe prescribing data before and after guideline implementation	Retrospective, cohort	NRTI Rx, patient demographics, patient allergies, diagnosis codes, and labs extracted from EMR	Assessed the proportions of veterans satisfying criteria pre- and post-implementation of criteria; Assessed continued adherence to criteria over time after implementation	Target antiretroviral medications prescribed >70% in accordance with VHA guidelines.
de Jong[25]	Clinical	Outpatient	To determine whether computerized DSSs can influence general practitioner prescribing (adherence to clinical guidelines)	Secondary analysis of previous study data	1 year EMR data from 103 practices collected into Second Dutch National Survey of General Practice: contains prescriptions, diagnoses, patient demographics, and DDS advice for 172 diagnoses	(1) Whether Rx was in accordance with advice of DSS. (2) The variation in prescriptions among GPs who use the DSS, using HHI	GPs who use the DSS daily prescribe more according to the advice given in the DSS than GPs who do not use the DSS (89% versus 75%, $P = 0.04$). No significant difference between the HHIs for both groups.
Donyai[26]	Medication errors	Inpatient	To investigate the effects of eRx on prescribing quality, as indicated by prescribing errors and pharmacists' clinical	Time series – before, after	eRx-system contained drug dictionary and suggestion of default doses (pharmacists counted number of medication orders and recorded errors manually)	Whether eRx reduced pharmacist interventions and prescribing errors. Record of other kinds of error introduced.	Following the introduction of eRx, there was a significant reduction in both pharmacists' interventions and prescribing errors. Interventions reduced from 3.0% of all medication orders to 1.9%, and errors reduced from 3.8% to 2.0%.

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Study	Setting	Objective	Design	Data source	Outcome measures	Results
Eguale[19]	Outpatient	To determine accuracy of eRx and drug management system in documenting orders for discontinuations and dose changes of Rx drug therapy and to identify reasons for drug discontinuations and dose changes	Prospective	eRx (MOXXI) versus chart review – patients with electronic drug discontinuations or dose-change orders	Accuracy of drug discontinuations and dose-change orders documented in eRx and drug management system; Reasons for discontinuations and dose changes	interventions, in a UK hospital surgical ward. eRx concordance with chart review was 80.8%–95.2%. Ineffective treatment, adjusting dose to optimize therapy and ADRs were most common reasons for therapy change. Sensitivity of eRx in identifying physician initiated discontinuation and dose changes was 67.0% (95% CI: 54.1–7737), specificity was 99.7% (95% CI: 99.5–99.9).
Fischer[27]	Outpatient	To find out if eRx with formulary decision support helps prescribers prescribe lower-cost medications and to contain health care costs	Pre-post intervention	eRx-prescriber ID, patient ID, prescription date, drug name, dosage, form, insurance plan	(1) Change in proportion of Rx for 3 formulary tiers before and after eRx. (2) Effect of eRx when controlling for baseline differences between intervention and control prescribers using multivariate longitudinal models. (3) Potential savings using average median cost by formulary tier	3.3% increase in tier 1 prescribing, with corresponding decrease in tiers 2 and 3 (brand name tiers). eRx accounted for 20% of filled Rx in intervention group.
Fischer[28]	Outpatient	To determine first-fill failure/primary non adherence in community-based practices as well as its predictors.	Cohort study	eRx and pharmacy claims	Rate of first-fill failure/primary medication non adherence	First-fill failure rate = 22% (151,837/195,930 prescriptions). Rate was higher at 28% when only new medications were considered and for newly prescribed medications for diabetes (31.4%), hypertension (28.4%), and dyslipidemia (28.2%).
Fox[29]	Outpatient	To compare the effectiveness of RSV with other statins on lowering LDL and goal attainment among patients with Types 1 and 2 diabetes	Retrospective, observation	EMR (GEMS database)-extracted ICD-9 codes, glucose levels, LDL, age, gender, smoking, BP, prescriptions for statins, and comorbid conditions	(1) Percent reduction in LDL (2) Percentage of patients attaining LDL goal less than 100 mg/dL	Significantly greater % LDL reduction (P < 0.0001) with RSV (28.4%) compared with other statins (13.7%–22.5%) and greater proportion (P < 0.05) attaining goal LDL (< 100 mg/dL) with RSV (72.8%) versus other statins (36.8%–67.4%).

Table 3 (*Continued*)

Reference	Research area	Practice setting	Study objective	Study design	Data elements	Outcome measures	Results
Franklin[30]	Medication errors	Inpatient	To assess the impact of a closed-loop eRx automated dispensing, barcode patient identification, and eMAR system on prescribing and administration errors, confirmation of patient identity before administration, and staff time	Time series – before, after	eRx within system (automated dispensing, barcode patient ID, and eMARs) – pharmacist identified errors, not through eRx system	% of new medication orders with a prescribing error, % of doses with medication administration errors, and % given without checking patient identity. Time spent prescribing and providing a ward pharmacy service as well as nursing time on medication tasks.	Prescribing errors identified in 3.8% of medication orders pre-intervention and 2.0% of orders afterwards ($P < 0.001$). Medication adverse events occurred in 7.0% of pre-intervention and 4.3% afterwards ($P = 0.005$). Time to prescribe regular inpatient medication increased while time decreased to administer medication.
Fretheim[31]	Clinical	Outpatient	To evaluate the effects of a tailored intervention to support the implementation of systematically developed guidelines for the use of antihypertensive and cholesterol-lowering drugs for the primary prevention of cardiovascular disease	Unblinded, cluster-randomized trial	EMR providing the number of thiazide prescriptions, cardiovascular risk assessment, and achievement of treatment goals for hypertension and cholesterol	Main outcomes: Proportions of (1) first-time prescriptions for hypertension where thiazides were prescribed, (2) patients assessed for cardiovascular risk before prescribing, and (3) patients achieving recommended treatment goals.	This article discussed the methodology and not the results of the intervention.
Hunteman[32]	Allergy alerts	Inpatient	To estimate the proportion of allergy alerts issued within computerized prescriber-order-entry, the frequency of the allergy-alert overrides, and the proportion of allergy-alert overrides according to prescriber override rationale	Retrospective, observation	Data extracted from CPOE – total number of prescription orders, number of prescriptions triggering allergy alerts, allergy alert overrides, override rationale, and patients' demographic information	Analysis of the number of allergy alerts, allergy alert overrides, and override rationales triggered by the CPOE system	Allergy alerts were triggered on 1.3% of order. Overall, 97% of alerts were overridden because: patient previously tolerated the medication (49%), benefit outweighed risk (29%), medication was therapeutically appropriate (24%), and free text explanations (8%).

Isaac[33]	Medication errors	Outpatient	To determine whether drug allergy and drug interaction alerts offered by clinical decision support is accepted by clinicians and whether it is based on the alert type, severity, or the class of medication	Retrospective, observation	Retrieved alerts generated by eRx system, containing drug name and class, alert type, interacting drug or class, alert severity, action taken in response to alert, as well as clinician and patient characteristics	% medical alerts overrode by prescribers and types of medical alerts	6.6% of electronic prescription attempts generated alerts. Clinicians accepted 9.2% of drug interaction alerts and 23.0% of allergy alerts. High severity interactions accounted for most alerts (61.6%) and clinicians accepted high-severity alerts slightly more often than moderate- or low-severity interaction alerts (10.4%, 7.3%, and 7.1%), respectively ($P < 0.001$).
Jani[15]	Medication errors	Outpatient	To assess the effect of an eRx system on the incidence and type of prescribing errors and the number of error-free visits	Time series – before, after	eRx system – medical administration, prescribing, and patient variables (allergy, weight, dose, route are mandatory), but not linked to clinical data, labs, or medical notes	Incidence and type of errors: % of prescriptions with missing essential items (allergy details, patient's weight, dose, and route) or were judged illegible	Overall prescribing error rate = 77.4% (95% CI: 75.3%–79.4%) for handwritten items and 4.8% (95% CI: 3.4%–6.7%) with eRx. Decreased rates of missing essential information and prescriptions judged illegible. The number of error-free patient visits that were error-free increased from 21% to 90% (69% difference; 95% CI: 64%–73.4%) after eRx.
Lagu[34]	Adherence	Outpatient	To evaluate the extent of patient failure to fill antihypertensive Rx and test hypothesis that presence of non-cardiovascular disease is negatively associated with filling antihypertensive Rx, and that presence of cardiovascular is positively associated with filling antihypertensive Rx	Cross-sectional	eRx – new or renewed antihypertensive medications, demographics, insurance status, diagnosis, physiologic measures, lab tests, and other prescribed medications	% of new or renewed antihypertensive medications matched with an insurance claim for the same generic drug	75.1% of eRx were filled. Prescriptions written for persons with 5 or more noncardiovascular comorbidities were significantly more likely to be filled (adjusted OR, 1.59; 95% CI: 1.07 ± 2.36) versus those for persons with fewer noncardiovascular comorbidities.
Owen[35]	Clinical	Inpatient and Outpatient	Addresses the feasibility and validity of using data electronically extracted from the VHA computer database (VistA) to monitor adherence to evidence-based recommendations for	Randomized	VHA EMR VistA- dates, global assessment of functioning, diagnostic codes, inpatient and outpatient prescription records, drug data, progress notes, laboratory	First study: (1) Whether the patient was prescribed an antipsychotic medication, (2) whether the patient received depot antipsychotic medication injections, and (3) whether the antipsychotic dose prescribed was concordant with treatment guidelines for schizophrenia	According to both medical record review and VistA data, about 25% of both inpatients and outpatients were receiving doses of antipsychotic medication above the guideline-recommended range. But VistA data contained less documentation of long acting depot injections compared with medical charting.

(Continued)

Table 3 (*Continued*)

Reference	Research area	Practice setting	Study objective	Study design	Data elements	Outcome measures	Results
			antipsychotic dosing for inpatient and outpatient treatment of schizophrenia		data; CPRS (more user friendly version of VistA) – progress notes and medication orders. Aggregate VistA data from 10 VHA centers stored into data warehouse monthly – inpatient and outpatient services, radiographic and surgical procedures, diagnostic codes, laboratory results, outpatient prescriptions, and patient demographics. Authors compared automated data extraction from data warehouse with manual progress notes reviewed from CPRS.		
Ross[36]	Utilization	Outpatient	To assess the effects of eRx on formulary compliance and generic utilization using managed care organization data	Retrospective	E-prescribers (system provides drug and formulary, eRx submission) versus traditional prescribers matched based on pharmacy claims, number of members, categories of drugs, and physician specialty (not all eRx)	Proportion of claims classified as formulary by each study group and formulary compliance was assessed in both groups and nationwide. Results of qualitative survey.	Both predominantly e-prescribers and traditional prescribers demonstrated high levels of formulary compliance, 83.2% versus 82.8%, respectively ($P = 0.32$) with no difference in generic drug utilization rates. Qualitative survey responses indicated reductions in calls both to and from pharmacies for prescription orders.
Shah[37]	Adherence	Outpatient	To assess the proportion of patients who fill their initial prescription for a	Retrospective, cohort	EHR data: patient demographics, date of diabetes diagnosis, number of refills,	Proportion of naïve prescriptions filled by patients within 30 days of prescription order date and	First-fill failure rate was 15% for antidiabetic medications. Copayments < US$10 (OR 2.22, 95% CI: 1.57–3.14) and baseline glycohemoglobin

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Author	Setting	Study design	Objective	Variables	Outcome measure	Results
			diabetes medication, understand characteristics associated with prescription first-fill rates, and examine the effect of first-fill rates on subsequent glycohemoglobin levels	drug class, number of comorbid conditions, number of office visits, glycohemoglobin lab results, date of Rx order; Pharmacy Data- drug class, copayment, order date, whether the Rx was filled, fill date	characteristics related with first-fill.	>9% (OR 2.63, 95% CI: 1.35, 5.09) were associated with improved first-fill rates while sex, age, and co-morbidity score had no association. Patients who filled their antidiabetic medications had significantly greater reductions in levels than those who failed to fill.
Shah[38]	Outpatient	Retrospective, cohort	To assess the proportion of patients with incident hypertension who filled a naïve prescription for antihypertensive drugs and to understand characteristics associated with first-fill rates	EHR data: patient demographics, number of refills, drug class, number of prescriptions, number of comorbid conditions, number of office visits, BP values; Pharmacy Data- drug class, copayment, date of Rx order, whether the Rx was filled, and date Rx filled	Proportion of patients with incident hypertension who filled a naïve prescription for antihypertensive drugs and patient characteristics associated with first-fill	17% first-fill failure rate for new, first-time prescriptions for an antihypertensive medication. Sex, age, therapeutic class, number of other medications prescribed within 10 days of the antihypertensive prescription, number of refills, co-pay, comorbidity score, baseline BP, and change in BP were significantly associated with first-fill rates ($P < 0.05$).
Singh[39]	Inpatient	Prospective	To describe errors and potential harm of inconsistent communication occurring within prescriptions entered through an advanced CPOE system and to identify predictive variables associated with inconsistent communication and potential harm in an advanced CPOE so as to identify safety improvements	Electronically retrieved all prescriptions with comments in free-text field from CPOE system; randomly selected 500 for manual review. Manually look for inconsistencies btw free-text and structured entry fields. Data collection form capturing type of medication, setting, nature of the inconsistency in errors, and potentially predictive variables.	Percent of prescriptions with inconsistencies and whether the error caused by the inconsistency resulted in harm	0.95% of new Rx contained inconsistent communication (comparable to unreported group). The most common element was dosage. Inpatient setting (OR 3.30; 95% CI: = 2.18–5) and surgical subspecialty (OR 2.45; 95% CI: = 1.57–3.82) associated with more errors.

Table 3 (*Continued*)

Reference	Research area	Practice setting	Study objective	Study design	Data elements	Outcome measures	Results
Smith[40]	Clinical	Outpatient	To examine the effects of CPOE with CDS in reducing the use of potentially contraindicated agents in elderly patients	Time series – before, after	EMR with CDS alerts on nonpreferred agents; patient demographics	Trend of number of non-preferred and preferred Rx dispensed per 10,000 members per month using interrupted time series analysis and which nonpreferred agents were used	Among elderly, use of nonpreferred agents decreased by 5.1 Rx per 10,000 ($P < 0.01$) which was a 22% relative decrease from the month before, and was sustained over 2 years of study. Although nonpreferred medications decreased for elderly, no offsetting increase in preferred medications was seen.
Steele[41]	Medication errors	Outpatient	To determine the impact of automated alerts by CPOE systems on medical errors related to drug-lab interactions in the primary care setting	Time series – before, after	EMR with CPOE (med and lab orders)- patient demographics, medications, and labs from CPOE system	Number of medication orders not completed and the number of rule-associated laboratory test orders initiated after alert display. Adverse drug events were assessed by doing a random sample of chart reviews using the Naranjo scoring scale.	During the postintervention period, an alert was displayed 5.6% for "missing laboratory values," 6.0% for "abnormal laboratory values", and 0.2% for both types of alerts. Focusing on 18 high-volume/high-risk medications, there was a significant increase in the percentage of time the provider stopped the ordering process and did not complete the medication order when an alert for an abnormal rule-associated laboratory result was displayed (5.6% versus 10.9% pre-post, $P = 0.03$). The provider also increased ordering of the rule-associated laboratory test when an alert was displayed (39% versus 51% pre-post, $P = 0.001$).
Taylor[42]	Medication errors	Outpatient	To identify what alerts physicians are seeing in outpatient settings and to build a better understanding of their perceptions of the value of alert systems	Observational	eRx (MOXXI-III) – identifies dosing errors, therapeutic duplications, drug interactions, potential toxicities, contraindications due to allergies, diseases, and age; documents clinical rationale used by physician in	Number of alerts generated and number of those requiring revisions	29% of 22419 Rx generated alerts, resulting in 14% that were revised. Most common were drug-disease alerts (41%).

Warholak[43]	Medication errors	Outpatient	To measure the incidence and nature of prescribing errors on electronic prescriptions that required active intervention by dispensing pharmacists to correct and to estimate the pharmacy personnel time and related practice expense required to resolve problems on prescriptions	Descriptive, cross-sectional	eRx (83% new, 17 refills), participating pharmacies reported interventions – did not extract electronic data	prescribing decisions (why start, stop, renew prescriptions); captures physicians response to alert / Number, type, and reason for pharmacist interventions on eRx	Pharmacists intervened on 3.8% of eRx. The most common reason for pharmacists' interventions was to supplement omitted information (31.9%), especially missing directions. Dosing errors were also quite common (17.7%). In most cases (56%), the e-Prescription order was changed and the prescription was ultimately dispensed. Pharmacists required an average of 6.07 minutes to conduct their interventions on problematic e-Prescription orders, representing an incremental dispensing cost of US$4.74.
Willig[44]	Medication errors	Outpatient	To assess the frequency of and factors associated with NRTI dosing errors in a university-based HIV clinic using electronic medical records focused on renal patients	Retrospective	Prescriptions, laboratory data, patient demographics (age, sex, weight, race)	Whether dosing errors are more common among renally impaired patients and whether the use of combination NRTIs would increase the risk for dosing errors in such patients. Clinical consequences of dosing errors	6% of NRTI prescriptions overall and 31% in renally impaired patients were dosed incorrectly. In generalized estimating equation-adjusted multivariable logistic regression analysis, didanosine use (OR, 11.51; 95% CI: 5.99–22.1), advancing age (OR, 1.75 per 10 years; 95% CI: 1.28–2.38 per 10 years), and minority race or ethnicity (OR, 2.69; 95% CI: 1.37–5.26) were associated with dosing errors.

Abbreviations: ADR, adverse drug reaction; BP, blood pressure; CDS, clinical decision support; CI, confidence interval; CPOE, computerized physician order entry; CPRS, computerized patient record-keeping system; DSS, decision support systems; EHR, electronic health record; eMAR, electronic medication administration record; EMR, electronic medical record; ePrescriber, electronic prescriber; ePrescription, electronic prescription; eRx, electronic prescribing; GEMS, General Electric Medical Systems; GP, general practitioner; HHI, Herfindahl–Hirschman index; HIV, human immunodeficiency virus; ICD-9, International Classification of Diseases, 9th Revision; ID, identifier; LDL, low-density lipoprotein; MOXXI, Medical Office of the 21st Century; NRTI, nucleoside reverse transcriptase inhibitor; OR, odds ratio; RR, relative risk; RSV, rosuvastatin; Rx, prescription; UK, United Kingdom; US$, United States dollars; VHA, Veterans Health Administration.

to a deidentified database of health care information, this will potentially increase the use of evidence-based medicine. For example, a query of a database on patients treated with a specific drug could identify patients with similar demographics/clinical characteristics (eg, age, co-morbidities) to allow for evaluation of effectiveness of first-line therapies, comparative treatments, and outcomes. This information would lead to highly individualized treatment, instead of the population-based evidence most clinicians have to go by now.

In addition, RCTs are more costly to conduct than other evaluation methodologies. Observational data from eRx and EMR, although not an alternative, can be a possible addition for testing drug efficacy in the future. Authors of a University of Pennsylvania study developed methodology to analyze EMR data for drug efficacy testing.[51] Even though the results do not suggest that studies using real-world electronic data can replace RCTs due to confounding, their study is the first of its kind and will encourage further research in this area.

With eRx data, adherence to first-fill treatments will be able to be studied.[28,37,38] A recently published and large study that evaluated data from a community-based eRx initiative included 75,589 patients treated by 1,217 prescribers.[28] The authors matched e-Prescriptions with pharmacy claims and found the first-fill failure rate for all e-Prescriptions was 22%. For newly prescribed common chronic conditions such as hypertension, dyslipidemia, and diabetes, first-fill failure rates were even higher and ranged from 28%–31%. Understanding population first-fill rates will provide opportunities (via the same HIT) to notify, survey, and analyze these first-fill failures which can then provide insight into MTMS interventions.

Personalized/point of care research

Eventually, eRx systems will be adopted at the point-of-care and can even be accessible to patients. Health care providers can use practice-based research to assess effectiveness of specific drug therapies in a "local population." Connected practice-based research networks can also address regional population management research. ERx and EMR systems with CDS can provide real-world analysis of current evidence-based guidelines, incorporating prescription information (first-fill rates, adherence, and persistence) into the analysis.

ERx systems can be designed to interface with the patient. Secure emails can be sent to patients reminding them about a prescription not picked up, upcoming appointments, and required follow-up or laboratory testing.

Between visits, patients can receive automatic notifications of preventive services, tests, or behavioral actions that are due or overdue to increase effectiveness of prescribed therapy. Patients can be given access to their own medication chart for medication reconciliation. In essence, eRx systems can be a centralized care management system for patients to coordinate their own care and help address requirements for MTMS. Highly sophisticated eRx systems can provide data resources with which to study the effectiveness of such MTMS programs.

It is unclear what the future holds; but one thing is certain – because prescription information is a vital part of the health care record, most if not all EMR systems will have eRx capabilities. Both patients and associated providers will have access to portable electronic versions of patient health care records. This plethora of information can be used by the regulatory officials to determine benefits and evaluate treatments, by physicians to evaluate and coordinate care, and by researchers to answer health care related questions. Certainly, research can satisfy some of the requirements for meaningful use prescribed by the government as criterion for subsidizing or funding the purchase of HIT.

Studies can evaluate evidence-based medicine using eRx alone and in combination with other data sources. These studies can provide additional information in support of evidence-based guidelines, and this application of eRx data allows research to cross the spectrum from RCTs to real-world outcome studies based in practices.

Conclusion

Although eRx is a relatively new data source, especially in community settings, it provides promise for practitioners to contribute to outcomes research, improve performance, and gather insight into publicly reported parameters. Clinical quality improvement and patient safety considerations will now be able to more easily tie into cost and comparative effectiveness research data offering tremendous opportunities. Every step of the eRx process can be tracked electronically and pooled into a centralized data source, enabling researchers to query for relevant data much more quickly, easily, and at a lower cost. It will no longer be a question of where to get the information, but asking the right questions in order to find the answers.

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