

Northwestern University
TOP-MEDS CERT: Tools for Optimizing Medication Safety
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Abstract

Purpose

Our center sought to improve patient safety by developing tools for safer medication use. The objective was to develop and test tools in four areas: statistical methods for studies of drug safety and effectiveness, opioid prescribing for acute pain, preventing and detecting drug name confusions, and patient-centered drug information.

Scope

Drug therapy is the most common medical service patients receive, but it is plagued by risks. Patients are exposed to drugs whose risks are poorly understood. High risk drugs such as opioids are frequently selected and dosed improperly. Drug name confusion causes patients to receive the wrong drugs. Consumers use drugs unsafely because drug information is poorly designed and confusing. To address these problems, we developed and ran a patient safety CERT focused on Tools for Optimizing Medication Safety (TOP-MEDS).

Methods

We used a variety of methods across the four core projects, including statistical analysis of claims data sets, retrospective review of electronic medical records, simulation studies, prospective and retrospective observational studies, randomized trials, and psychological experiments.

Results

We had varying success across the projects. We were most successful in our statistical methods and drug name confusion projects. We built and tested our opioid simulator and demonstrated its effects as a teaching tool. Evidence of patient benefit is pending. Similarly, data from our health literacy randomized trial is still being analyzed, but preliminary results suggest a small or null patient benefit.

Key Words: Medication safety, adverse drug events, statistical methods, opioid dosing, simulation, drug name confusion, health literacy.

Purpose

The specific aims from the original application, briefly stated below, have not been modified.

1. Develop and apply a multivariate person-time logistic regression model for large-scale adverse drug event screening.
2. Improve the safety and effectiveness of inpatient acute pain care by developing and validating a web-based simulator to train prescribers in the proper selection and dosing of opioids.
3. Refine a standard battery of tests for pre-market safety screening of drug names, and develop and test methods for preventing and detecting drug name confusion errors in clinical databases.
4. Rigorously evaluate an EHR-based, low literacy strategy for promoting safe, effective prescription drug use among English and Spanish-speaking patients in an urban primary care setting.

Our Center has 4 main project areas as described above. We report progress in each of these areas below. Within each project area, we describe studies and results, significance and future plans. Overall, the four core projects are on schedule and on budget to be completed as planned, with some minor exceptions (e.g., slow recruitment into the health literacy trial and delayed start of the opioid simulator study) noted below.

Project 1: Innovative Statistical Methods for Large-Scale Drug/Adverse Event Screening

Purpose and Scope

Develop a Multivariate Person-time Logistic Regression Model for Large-Scale Drug-ADE screening: Given the limitations of spontaneous reporting systems (such as the FDA AERS), we plan to develop a method of Adverse Drug Effect (ADE) screening that uses more complete electronic datasets and benefits from the longitudinal nature of those data. This new analytic method compares the risk of an ADE on a month by month basis during months when the drug was taken versus months in which it was not taken, utilizing large medical records databases. The general methodology uses a variant of mixed-effects logistic regression models to obtain Drug-ADE specific risk estimates simultaneously for all Drug-ADE combinations (or a relevant class such as antidepressants and suicidal behaviors), adjusted for case-mix (e.g., age, sex, race, diagnosis, concomitant medications). The method will be based on marginal maximum likelihood and empirical Bayes estimation. A simplification of the model can be used to examine risk for a single Drug-ADE interaction. Statistical specification of the model in terms of random-effects distribution, linear versus non-linear relations (e.g., additive models for non-linear smoothing), and multiple comparison problems for correlated data will be fully explored.

Methods

Efron (1) noted the connection between survival analysis models and logistic regression models for survival data that are discrete or grouped within time intervals. In the context of drug safety, the discrete-time survival model allows us to use drug exposure as a time-varying covariate in estimating the hazard rate of an AE on a month-by-month basis. Unlike traditional analyses in which exposure is considered constant, treatment is evaluated on a month-by-month (or any other fixed time window) basis (i.e., each subject serves as his/her own control). Both proportional and non-proportional hazards models are available. Here, we extend the model described above to the case of large-scale screening of ADEs. To do so, we will define a clustering unit of patients who have taken drug A and experienced adverse event B. Depending on the number of drugs and AEs, there will be a total of $N=A*B$ clusters. With 100 drugs and 100 AEs, there will be 10,000 potential ADEs. The analysis proceeds as described above in which we are comparing periods of drug exposure to non-exposure, but we add random-effects to the model to obtain cluster-specific effects which describe the deviation of the kth ADE from the overall ADE rate across all N ADEs examined. Relevant covariates such as time, age, sex, prior AEs can also be included as random effects so that they too take on ADE-specific interpretations. A computational problem arises in evaluating the likelihood of this non-linear mixed-effects regression model in that the degree of integration is equal to the number of covariates+1. The traditional approach of adaptive quadrature, is typically limited to approximately 5 random effects; however, we expect that there may be cases in which the number of relevant covariates used even for large-scale screening

purposes may be considerably larger than 5. To this end, we propose to explore new methods for evaluating the likelihood of the non-linear mixed-effects regression models.

For the j th subject taking the i th drug, denote the grouped survival time variable by T_{ij} and covariate by X_{ij} . The discrete-time hazard rate λ_{ijt} is defined as: $\lambda_{ijt} = Pr(T_{ij} = t | T_{ij} \geq t, X_{ij})$. Then $Pr(T_{ij} \geq t) = \prod_{k=1}^t (1 - \lambda_{ijk})$ and $Pr(T_{ij} = t) = \lambda_{ijt} \prod_{k=1}^{t-1} (1 - \lambda_{ijk})$. Let δ_{ij} be the event indicator taking the value of 1 if an event occurs at $T_{ij} = t_{ij}$, and 0 otherwise. The likelihood can be written as

$$L = \prod_i \prod_j [Pr(T_{ij} = t_{ij})]^{\delta_{ij}} [Pr(T_{ij} > t_{ij})]^{1 - \delta_{ij}} = \prod_i \prod_j \prod_{k=1}^{t_{ij}} \left[\left(\frac{\lambda_{ijk}}{1 - \lambda_{ijk}} \right)^{y_{ijk}} (1 - \lambda_{ijk}) \right],$$

where $y_{ijk} = 1$ if the j th subject taking the i th drug experienced an event at time $T_{ij} = k$, and 0 otherwise.

This likelihood has the same expression as that of a binary model with probabilities λ_{ijk} . Therefore, discrete time survival data can be modeled with logistic regression models with either a logit (odds ratio) or a complimentary log-log (hazard ratio) link, i.e. $\log(-\log(\lambda_{ijk})) = \alpha_k + \beta^T X_{ij}$, where β is the coefficient vector for covariates X_{ij} , and α_k is related to the baseline survival probability in the interval defined by $T_{ij} = k$ at $X_{ij} = 0$ (2). We note that the ADE effect as well as ADE-specific covariate effects are correlated for people taking the same drug and experiencing the same AE. For this reason we introduce random effects to account for between cluster (ADE) variability. We write the event probability, taking into consideration the random effects, as $\log(-\log(\lambda_{ijk})) = \alpha_k + \beta^T X_{ij} + \gamma^T Z_i$, where γ is the vector of random effects and Z_i is the design vector for random effects of the i th ADE. The conditional likelihood for the i th ADE, given the random effects, is

$$g(y_i | \gamma_i; \beta) = \prod_j \prod_{k=1}^{t_{ij}} \left[\left(\frac{\lambda_{ijk}}{1 - \lambda_{ijk}} \right)^{y_{ijk}} (1 - \lambda_{ijk}) \right]$$

The marginal likelihood for the i th drug is the integral of the conditional likelihood over the distribution of random effects $p(\gamma_i; \beta)$, assuming $\gamma_i \sim N(\mathbf{0}, \theta)$. That is $L_i(\beta, \theta) = \int g(y_i | \gamma_i; \beta) p(\gamma_i; \theta) d\gamma_i$. The parameter estimates of (β, θ) may be obtained by maximizing the marginal likelihood. Since the integral cannot be evaluated analytically, numerical methods are usually involved in approximating the marginal likelihood.

As the number of random effects becomes larger than 5, the use of adaptive quadrature to evaluate the marginal likelihood is no longer practical. Two alternative approximations are Laplace and Maximum a posteriori (MAP). Unlike the quadrature methods which performs direct numerical integration, the Laplace method uses a Taylor series expansion of the integrand to bypass the integration. Using this method, the marginal likelihood can be expressed as $L_i(\beta, \theta) = c \int e^{h(\gamma_i)} d\gamma_i$,

where

$$c = (2\pi)^{-\frac{n_i}{2}} |\Sigma|^{-\frac{1}{2}}, \text{ and } h(\gamma_i) = \log[g(y_i | \gamma_i; \beta)] - \frac{1}{2} \gamma_i^T \Sigma^{-1} \gamma_i.$$

When the cluster size is large, then a second-order Laplace approximation yields the marginal log-likelihood

$$l_i(\beta, \theta) \approx C + \frac{n_i}{2} \log(2\pi) + h(\tilde{\gamma}_i) - \frac{1}{2} \log |h''(\tilde{\gamma}_i)|,$$

where $\tilde{\gamma}_i$ is the mode of $h(\gamma_i)$. The Laplace method approximates the integral with the objective function expanded at the mode, leading to asymptotically unbiased estimates. The accuracy of the Laplace's method depends on the number of terms used in the Taylor series expansion.

In Bayesian statistics, a maximum *a posteriori* (MAP) estimate is the mode of the posterior distribution. Unlike the frequentist method of maximum likelihood, MAP incorporates a prior distribution over the quantity of interest in the objective function. MAP estimation for nonlinear mixed-effects models was first proposed by McGilchrist (3). Instead of treating β and $\Sigma(\theta)$ as parameters in the frequentist approaches, MAP considers β and γ as parameters and $\Sigma(\theta)$ as a prior covariance matrix for γ . One then maximizes the log posterior likelihood, which can be written as $l(\beta, \gamma, \Sigma(\theta)) = l(\beta, \gamma) + l(\Sigma(\theta))$. Estimates can be obtained by an iterative process. At iteration t , $\hat{\beta}^{(t)}$ and $\hat{\gamma}^{(t)}$ are set to maximize $l(\beta, \gamma)$ and $l(\beta, \gamma, \Sigma(\theta))$ with current estimates of other parameters, and $\hat{\Sigma}(\theta)^{(t)}$ may be obtained from $\hat{\gamma}^{(t)}$.

Results

- We showed that MAP estimates perform extremely well in drug safety settings where the number of clusters (ADEs) and number of subjects are both large ($m=n>100$).
- We have integrated the MAP estimators into the SuperMix program which will make routine application of this new methodology accessible to pharmacoepidemiologic researchers and statisticians interested in drug safety.
- Developing a reliable system for rapid identification of potential signals of serious adverse events in a timely fashion is an important task in conducting post-marketing surveillance. Through the development of DRUGStat, a robust system of signal detection can be implemented in a more efficient and effective manner. The power of DRUGStat lies in its ability to easily compare whether a certain drug is potentially harmful compared to a host of other drugs in a specific class of interest. In addition, a specific adverse event over a specific time windows for a particular drug of interest can be evaluated. The DRUGStat Program is now freely available for routine application at <http://www.healthstats.org/drugstat.html>.
- The work described to this point is designed to generate signals that can be verified using more focused analyses of a particular ADR. Moving from observation to causation we have developed an extension of our discrete time survival model that uses marginal structural models (Robins, 2000) to provide the equivalent of a sequentially randomized trial out of a longitudinal observational dataset. A paper that illustrates the use of marginal structural models for examining the dynamic association between antidepressants and suicide attempts in children using the LifeLink database as well as MarketScan database has now been published.
- Gibbons, R.D., Coca-Perrillon, M., Hur, K., Conti, R.M., Valuck, R.J., Brent, D.A. Antidepressant treatment and suicide attempts and self-inflicted injury in children and adolescents. *Pharmacoepidemiology and Drug Safety*, 24, 208-214, 2015.
- **Statistical Methods for Drug Safety:** Robert D. Gibbons and Anup Amatya. Chapman and Hall, 2015.
Description of textbook: This text presents and describes methods for analysis of pharmacoepidemiologic data, with a strong emphasis on application of these methods to problems in the pharmacovigilance and drug safety. Two audiences are envisioned for this book. The first is applied statisticians working in the field of pharmacoepidemiology, while the second is students in applied statistical programs, second year masters and doctoral students. Special statistical procedures that are described include: Bayesian Neural Network, Multi-item gamma Poisson shrinker, linear and nonlinear mixed models, and discrete-time logistic regression models, and methods for minimizing bias and deriving causal inference from observational data. In non-technical language, this book is important because safety of pharmaceutical product rely heavily on the post-marketing data and the literature. In order to analyze those high dimensional data, analysts must

be familiar with the novel analytic methods and the statistical theories behind them. Thus, this book is geared towards both users and developers of statistics.

- High Dimensional Empirical Bayes Screening (HDEBS): Our final work on this grant was to develop a large-scale ADR screening system and illustrate its application to the problem of better understanding the risks and benefits of drugs on self-harm.

Suicide is both rare and the tenth leading cause of death in the United States. The effect of many medications on suicide risk is intensely debated. Traditional approaches to pharmacovigilance largely involve analysis of spontaneous reports with numerous scientific limitations. We developed a statistical surveillance methodology based on large-scale medical claims data that identifies drugs that increase and decrease the risk of suicidal events. The methodology is applicable to any adverse event (e.g. myocardial infarction) or combination of events (e.g. any cardiovascular event) and can provide simultaneous analysis of a million or more potential adverse drug reactions.

Analysis of suicide attempts and self-harm for 949 drugs revealed 9 drugs associated with increased risk and 28 drugs associated with decreased risk. Among the highest risk drugs were carisoprodol and alprazolam and among the most protective were mirtazapine and folic acid.

High-dimensional drug safety surveillance using high quality observational data is possible and generates several important signal regarding drugs and suicide risk.

Publications

Gibbons R.D., Hur K., Brown C.H., Davis J.M., Mann J.J. Benefits from antidepressants: Synthesis of 6-week patient-level outcomes from double-blind placebo controlled randomized trials of fluoxetine and venlafaxine. *Archives of General Psychiatry*, 69, 572-579, 2012.

Gibbons R.D., Brown C.H., Hur K., Davis J.M., Mann J.J. Suicidal thoughts and behavior with antidepressant treatment: Re-analysis of the Randomized Placebo Controlled Studies of Fluoxetine and Venlafaxine. *Archives of General Psychiatry*, 69, 580-587, 2012.

Gibbons R.D. and Amatya A. *Statistical Methods for Drug Safety*. London, Chapman and Hall, 2015.

Gibbons, R.D., Coca-Perrillon, M., Hur, K., Conti, R.M., Valuck, R.J., Brent, D.A. Antidepressant treatment and suicide attempts and self-inflicted injury in children and adolescents. *Pharmacoepidemiology and Drug Safety*, 24, 208-214, 2015.

Project Area 2: Simulation Training to Improve the Safety of Inpatient Opioid Use

2.A. Overall Purpose and Scope

The long term objective is to improve the safety and effectiveness of pain care for hospitalized patients with acute or acute exacerbation of chronic pain. The short term objective is to develop and test a method for training hospital-based practitioners in principles of safe and effective pain care. We will achieve these objectives by carrying out studies with the following specific aims: (1) to refine and port to the Web an existing computer-based simulation training tool that allows clinicians to learn the relationship between opioid selection and dosing and resulting changes in the trajectory of pain scores; (2) to identify and refine measures of effective pain care and opioid-related adverse drug events (ADEs) in the hospital setting; and (3) to evaluate the effect of simulation training on safety and effectiveness outcomes using an interrupted time series design.

2.B. Studies

2.B.1. Analysis of Pain Score Trajectories

Purpose. Pain care for hospitalized patients is often suboptimal. Representing pain scores as a graphical trajectory may provide insights into the understanding and treatment of pain.

Methods. We describe a 1-year, retrospective, observational study to characterize pain trajectories of hospitalized adults during the first 48 hours after admission at an urban academic medical center. Using a subgroup of patients who presented with significant pain (pain score > 4; n = 7762 encounters), we characterized pain trajectories and measured area under the curve, slope of the trajectory for the first 2 hours after admission, and pain intensity at plateau. We used mixed-effects regression to assess the association between pain score and sociodemographics (age, race, and gender), pain medication orders (opioids, nonopioids, and no medications), and medical service (obstetrics, psychiatry, surgery, sickle cell, intensive care unit, and medicine). K-means clustering was used to identify patient subgroups with similar trajectories.

Results. Trajectories showed differences based on race, gender, service, and initial pain score. Patients presumed to have dissimilar pain experiences (eg, sickle vs obstetrical) had markedly different pain trajectories. Patients with higher initial pain had a more rapid reduction during their first 2 hours of treatment. Pain reduction achieved in the 48 hours after admission was approximately 50% of the initial pain, regardless of the initial pain. Most patients' pain failed to fully resolve, plateauing at a pain score of 4 or greater. Visualizing pain scores as graphical trajectories illustrates the dynamic variability in pain, highlighting pain responses over a period of observation, and may yield new insights for quality improvement and research.

Publication

Kannampallil, T., Galanter, W. L., Falck, S., Gaunt, M. J., Gibbons, R. D., McNutt, R., . . . Lambert, B. L. (2016). Characterizing the pain score trajectories of hospitalized adult medical and surgical patients: a retrospective cohort study. *Pain*. doi:10.1097/j.pain.0000000000000693

2.B.2 Effect of Simulation on Learner Outcomes

Purpose: To evaluate the efficacy of an internet-based opioid dosing simulator to teach medical residents how to manage pain in the inpatient setting.

Scope. Nearly 50% of hospitalized patients receive opioids. However, there is a lack of consensus regarding evidence-based guidelines or training programs for safe and effective management of pain in the hospital.

Methods. This was a prospective, longitudinal observational study. The intervention was training on an internet-based opioid dosing simulator. Participants were 120 family medicine and internal medicine residents at a large, urban, academic medical center.

In face-to-face didactic sessions, we taught residents conceptual principles of pain management and how to use the simulator. After training, each resident independently completed 10 training and, subsequently, 5 testing trials on the simulator. For each trial, we collected medications, doses, routes and times of administration, pain scores, and an overall summary score. We used mixed-effects regression models to assess the impact of simulation training on performance scores, variability in pain score trajectories, appropriate use of short- and long-acting opioids, and the use of naloxone.

Results. Residents completed 1,582 simulation trials (M=13.2, SD= 6.8), with sustained improvements in their simulated pain management practices. Over time, residents improved their overall pain management scores (b=0.05, p<.0001), generated lower mean pain score trajectories with less variability (b=-0.02, p< 0.0001), switched more rapidly from short-acting to long-acting agents (b=-0.50, p< 0.0001), and used naloxone less often (b=-0.10, p<0.0001). Residents translated their understanding of didactically presented principles of pain management to their performance on simulated patient cases. Given the widespread use of simulators in medical education, simulation may present opportunities for effective acute pain management.

Publication. The manuscript is in preparation, to be submitted to the *Journal of Hospital Medicine*.

2.B.3. Effect of Simulation Training on Clinical Outcomes

This study examines the effect of simulation training on pain scores and on adverse event rates. The main adverse events are death, transfer to the ICU, rapid response activation, use of naloxone, sedation score, constipation and urinary retention. The design is an interrupted time series with control condition. Intervention participants are those who received simulation training, with the intervention date being the date they completed the training. The control group includes residents in the same programs who did not receive training. There are significant challenges in associating patients with clinicians since each patient typically receives care from multiple clinicians. Data analysis for this study is still underway. Final results will be published separately.

Project Area 3. Predicting and Detecting Drug Name Confusion Errors

3.A. Purpose and Scope

The specific aims are unchanged from the original application.

1. Develop, demonstrate and disseminate a standard protocol for pre-approval testing of drug names, including a standard battery of psycholinguistic tests, computer searches, and data analytic methods, all with comparison to control names. The achievement of this aim will provide both regulators and pharmaceutical manufacturers with a scientifically validated, step-by-step method for testing new drug names for confusability.
2. Develop and test a method for detecting drug name confusion errors in EMR data. The achievement of this aim will provide regulators with a method for making population estimates about the incidence of certain types of drug name confusions, and it will allow for the mitigation of harm when wrong drug errors are detected soon after they are made.
3. Determine whether CPOE indication prompts can provide a patient safety error check as a side effect. The achievement of this aim will enable us to understand whether an intervention designed for another purpose (i.e., to improve the quality of a problem list) might have the capability of preventing drug name confusions by reminding prescribers of the indications for the drugs they are ordering.

3.B. Methods and Results

We describe the results in three sections, each devoted to one of the specific aims above.

3.B.1 Aim 1. Develop and Test Pre-Approval Protocol

This section describes progress on a psycholinguistic studies of look-alike and sound-alike drug name confusion errors. The purpose of the study is to determine if a drug name's error rate on perception and memory tests can predict that drug name's real-world error rate. We hypothesized that perception and memory tests would effectively predict real-world error rates given that drug name confusion errors are often caused in part by lapses in perception and memory. If the psycholinguistic tests are shown to predict real-world error rates, then they can be used as part of a pre-approval protocol to identify drug names that are likely to be confusable and therefore should not enter the marketplace.

Study 1

Purpose and Scope

Drug name confusion is a common type of medication error and a persistent threat to patient safety. In the United States, roughly one per thousand prescriptions results in the wrong drug being filled, and most of these errors involve drug names that look or sound alike. Prior to approval, drug names undergo a variety of tests to assess their potential for confusability, but none of these pre-approval tests has been shown to predict real-world error rates. We conducted a study to assess the association between real-world drug name confusion error rates and laboratory-based tests of drug name memory and perception.

Methods

Eighty participants, including doctors, nurses, pharmacists, technicians, and lay people, completed a battery of laboratory tests assessing visual perception, auditory perception, and short-term memory of drug name pairs (for example, hydroxyzine/hydralazine).

Results

Laboratory test error rates (and other metrics) significantly predicted real-world error rates obtained from a large, outpatient pharmacy system, with the best fitting model accounting for 37% of the variance in real-world error rates. Cross-validation analyses confirmed these results, showing that laboratory tests also predicted errors from a second pharmacy system, with 45% of the variance being explained by the laboratory test data.

Across two distinct pharmacy systems, there is a strong and significant association between drug name confusion error rates observed in the real world and those observed in laboratory-based tests of memory and perception. Regulators and drug companies seeking a validated pre-approval method for identifying confusing drug names ought to consider using these simple tests. By using a standard battery of memory and perception tests, it should be possible to reduce the number of confusing drug name pairs that reach the market, which will help protect patients from potentially harmful medication errors.

Publication

Schroeder, S. R., Salomon, M. M., Galanter, W. L., Schiff, G. D., Vaida, A. J., Gaunt, M. J., . . . Lambert, B. L. (2016). Cognitive tests predict real-world errors: the relationship between drug name confusion rates in laboratory-based memory and perception tests and corresponding error rates in large pharmacy chains. *BMJ Qual Saf.* doi:10.1136/bmjqs-2015-005099

Study 2

Purpose and Scope

In a previous study, we assessed whether the real-world error rates of look-alike sound-alike drug name pairs (such as hydroxyzine-hydralazine, clomiphene-clomipramine, and Zyrtec-Zantac) can be predicted by how many errors pharmacists, technicians, doctors, nurses, and patients make on those same drug name pairs on laboratory-based cognitive tests (i.e., tests that make it difficult for participants to accurately perceive and remember). The results indicated that indeed a drug name pair's performance on the cognitive tests significantly predicted its error rate in two large community pharmacy chains. The implication of this finding is that, during the pre-approval process, a proposed drug name can be submitted to these tests, and if it performs poorly, then the name can be rejected before it enters the market and threatens patient safety.

We decided to conduct a follow-up study for two reasons. The first reason is that, while the previous study suggests that cognitive tests can be used to predict error rates of drug name pairs (e.g., hydroxyzine-hydralazine), regulators and pharmaceutical companies may be more interested in a proposed drug name's overall error rate across all pairs (e.g., hydroxyzine's propensity to be confused not just for hydralazine but also for hydrocort, thorazine, etc.). The second reason is to attempt to replicate the concept that cognitive tests are useful for assessing a drug name's confusability.

Methods and Results

In the second study, using a very similar methodology to the first study, we assessed whether cognitive tests can predict overall error rates. Thirty-six participants (18 pharmacists and 18 pharmacy technicians) completed the cognitive tests. The cognitive tests included an auditory perception task, a visual perception task, and a short-term memory task. In each task, participants were assessed on 77 drug names, and they had to type in the name they saw or heard and then select the name from a drop-down menu. The results indicated that error rates on the tasks were positively correlated with real-world error rates (i.e., the more errors participants made on a particular drug name, the more errors that drug had in a real-world pharmacy chain), with Pearson's r correlations ranging from .16 to .40. Regression analyses indicated that the cognitive error rates significantly predicted the real-world error rates (adjusted $R^2 = .12$ and $R^2 = .18$). Though the predictive capacity was lower than in the first study, the second study provides corroborating evidence that cognitive tests can predict real-world error rates (both at the level of specific look-alike sound-alike pairs and the level of overall error rates). Taken together, these studies endorse the use of cognitive tests in assessing the safety of a proposed drug name.

Publication

Manuscript in preparation.

Study 3: Detection and Prediction Limits for Identifying Highly Confusable Drug Names from Experimental Data

Purpose

The purpose of this study was to develop and demonstrate rigorous statistical methods that will be used to support inferences about the confusability of proposed new drug names in experimental designs.

Scope

Confusions between drug names that look and sound alike are common, costly, harmful, and difficult to prevent. One prevention strategy is to screen proposed new drug names for confusability before approving them. Widespread acceptance of pre-approval tests of confusability is compromised by the lack of experimental designs and statistical methods to support valid inferences about whether a proposed new name is unacceptably confusing. One way of identifying confusing names is to conduct memory and perception experiments on a set of drug names which would include both the new name and a set of control names (e.g., names already on the market). The experiment would yield an observed error rate for every name. Inferences about the acceptability of the new name can be made by comparing the error rate of the new name to the distribution of error rates of the control names. We describe four memory and perception experiments on drug names, carried out using clinicians as participants. Each experiment included drug names designated as test and control names. We demonstrate how to use a combination of logistic regression, Poisson prediction limits, and highly assured credible intervals to identify and apply a threshold for identifying unacceptably confusing names. Our models show an excellent fit to the data. These experimental designs and analytic methods should be useful in the preapproval testing of proposed new drug names and in similar regulatory scenarios where it is necessary to draw inferences about the comparative safety or effectiveness of new versus old products.

Much of the raw data and detailed descriptions of the methods can be found at <http://www.icpsr.umich.edu/icpsrweb/ICPSR/studies/34122/version/1>. The Superlab code to run the experiments can be downloaded from <http://community.cedrus.com/forumdisplay.php?f=9>.

Methods

We analyzed data from four experiments that tested memory and perception of drug names.

In what follows we lay down the steps of how to detect new drug names that are more confusing compared to the existing drug names or in other words, new drugs that have potentially confusable names. A potentially confusable drug name is quantified by its error rates. In each experiment, the error rate of a drug

name is determined by the misspecification of its correct name by the participants. With the error rate (the complement of the error rate will be called as the accuracy rate) of a new drug name alone, we cannot decide whether it is potentially confusable. In order to determine the status of an experimental drug name, we compare its accuracy rate with those of existing drugs (referred to as control drugs) available in the market. The procedure of our comparison is based on a threshold value or a limit determined by using the distribution of accuracy rates of control drugs. Using the control drugs, we construct three different types of limits based on (i) mixed-effects logistic regression models, (ii) Poisson Distributions, and (iii) Bayesian Analysis. Next, we use those limits as thresholds to detect new drugs that have undesirable names. Details are given in the publication listed below.

Results

Drug name confusions are a common type of medication error, and they often have harmful effects. Preventing such errors is an important priority in patient safety research and practice. Subjecting new names to a series of memory and perception tests prior to approval is one method that has been proposed for identifying names with a high likelihood of being confused once they entered the market. One obstacle to the acceptance of these pre-approval testing methods has been the absence of validated experimental designs and statistical frameworks for making the types of inferences that are critical, i.e., inferences about whether a proposed new name is any more confusing than a valid sample of existing names. In this project we illustrated experimental designs (e.g., memory and perception experiments with test names and controls), and we developed a valid statistical framework. The statistical framework supports two types of inferences: (i) is the error rate for the test name different than that observed for the controls; and (ii) does the test name fall in the extreme range of the distribution of controls. Application of these analytic methods to the data demonstrated that the methods could identify some names that were known to be confusing (i.e., some of those which were previously removed from the market due to confusability) and could identify extreme areas of the distribution of error or accuracy rates that could be used as thresholds for the acceptability or unacceptability of proposed new drug names. We also demonstrated that the models provided an excellent fit to the observed data.

Although we demonstrated the usefulness of these methods in the specific domain of newly proposed drug names, we believe they may have general utility in a variety of regulatory scenarios. Whenever a new drug or device or regulated product has a measured characteristic (e.g., a failure rate) and there exists a population of previously approved products in the same category on which this characteristic can be or already has been measured, then it should be possible to use the methods described here to make valid inferences about the characteristic of the new product compared to that observed in the population of approved products. Consider the case of a new medical device such as an artificial hip or knee joint. Using the methods described here, the failure rate of a new device in clinical studies, or in the first year of real-world use, could be compared to the failure rate observed in the population of all other devices in the same category, allowing one to make inferences about the comparative safety or effectiveness of the new product compared to similar existing products.

Publications

Lambert, B. L., Bhaumik, R., Zhao, W., & Bhaumik, D. K. (2016). Detection and prediction limits for identifying highly confusable drug names from experimental data. *Journal of Biopharmaceutical Statistics*, 26(2), 365-385. doi:10.1080/10543406.2015.1052481

3.B.2 Aim 2. Develop and test wrong-drug error detection system

Study 1: Pilot Study Focusing on Cycloserine/Cyclosporine Confusions

Purpose

To demonstrate an automated system for detecting drug name confusion errors by describing a series of orders involving confusion between cycloserine and cyclosporine.

Scope

Confusions between medication names that look-alike and sound-alike (LASA) remain a common and costly type of medication error.¹ Although most cause minimal or no harm, such errors have the potential to seriously injure and even kill patients.^{2,3} One of the most significant challenges LASA errors pose is that they can occur during any stage of the medication-use process, including prescribing, order entry, dispensing, administration, and monitoring. Despite advances in computerized prescriber order entry (CPOE), wrong drug errors are still reported at a rate of roughly 1 per 1,000 prescriptions in both inpatient and outpatient settings.^{4,5} LASA errors are often not detected until they have reached the patient, increasing the probability of patient harm.^{4,6} We developed an automated system for identifying potential LASA errors that works by identifying mismatches between a drug's indications and the diagnoses in a patient's administrative record. Here we report how this technique identified a series of potentially harmful confusions between cyclosporine and cycloserine, and we recommend strategies for prevention.

Methods. We developed a computer algorithm that detects potential drug name confusion errors by analyzing medication orders and ICD9 diagnostic claims. The algorithm flags possible medication errors if three conditions occur: (1) a medication (Drug A) is ordered that is not justified by any diagnosis; (2) another medication exists (Drug B) whose similarity to Drug A exceeds a threshold; and (3) Drug B has an indication that matches an active diagnosis (e.g., when hydroXYzine is prescribed without a diagnosis of anxiety or itching in a patient who has a diagnosis of hypertension, confusion with hydrALAZINE is suspected). We identified 2 cases where cycloserine was ordered when cyclosporine was intended. We then reviewed all cycloserine orders over 7 years and found that 11 of 16 orders were meant to be cyclosporine. This prompted the placement of an alert when ordering cycloserine.

The algorithm and a more systematic test of its effectiveness will be described in a separate paper, but some additional detail can be offered here. Pseudo-code for the algorithm is given in Figure 1.

```

FOR each patient,
  FOR each Drug A that was prescribed only once,
    CHECK if Drug A is justified by a diagnosis in patient A's record
    IF Drug A is not justified
      FOR each Drug B in patient's prescription record,
        COMPUTE similarity between Drug A and Drug B.
        IF the similarity is above a given threshold
          AND Drug B appears in patient A's medication history
          OR an indication for Drug B appears in patient A's medical record
            REPORT that Drug A is a potential error and the possible correct Drug is Drug B
  
```

Figure 1. Pseudo-code for error detection algorithm.

The approach requires three types of data: medication orders, diagnostic claims, and drug indications. We extracted 10 years of medication order data from the electronic health record at the University of Illinois Hospital and Health Sciences system (UI-Health). We extracted ICD9 diagnoses data from administrative claims for the same time period. We licensed drug indication information from Thomson Reuters Healthcare. This database mapped generic drug names to free text descriptions which resembled SNOMED diagnosis labels. We used natural language pre-processing to map free text descriptions to proper SNOMED diagnostic codes, and then we mapped SNOMED codes to ICD9 using existing mappings. Finally, we manually refined

the accuracy and completeness of the drug indication database, focusing primarily on drugs that either appeared on the inpatient formulary or that were used commonly in our health system.

Results

Application of this algorithm to UI-Health identified many potential errors. Among these were two potential errors wherein cycloserine was ordered without a justifying indication in patients who did have an indication for cyclosporine. These charts were reviewed, and it was determined that cycloserine was, in fact, selected in error, and that the intended drug was cyclosporine. Several factors increase the risk of confusions between these two names. The BI-SIM has been shown to be the measure of similarity that gives the greatest accuracy when predicting drug name confusion, with a score range of 0.00 (least similar) to 1.00 (same). The BI-SIM score places emphasis of scoring on similarity found at the beginning of the drug names.⁷ This is an important consideration given that the risk of confusing two names will be increased if they appear in close proximity in a pick list (e.g., on an order entry screen) or if products are stored alphabetically in close proximity. Cycloserine and cyclosporine have a BI-SIM similarity score of 0.83.⁷ Also, when one drug is used much more often than the other, the likelihood of misperceiving the less commonly used drug increases.⁸ Finally, cyclosporine and cycloserine are adjacent to one another in the UI-Health CPOE screen (see Figure 2) and automatically populate consecutively in response to a search query (see Figure 3).

To further investigate this type of error, we searched for all prescriptions for cycloserine at UI Health between June 1, 2008 and December 31, 2014. The ratio of cyclosporine to cycloserine prescriptions during this period was roughly 1,100:1 when ophthalmologic and oral preparations were included and roughly 900:1 when only oral preparations were included. Because the detected error involved cycloserine being selected when cyclosporine was intended, and because cycloserine was prescribed much less frequently than cyclosporine, we focused only on cycloserine orders. There were a total of 16 orders for cycloserine in 16 unique patients during the period in question [see Table 1].

We reviewed the medical records of all 16 patients. In 5 of the 16 orders (31%), no medication error occurred. Cycloserine was the intended medication. In eleven of the 16 orders (69%), a LASA error occurred in which cycloserine was ordered when cyclosporine was indicated and apparently intended. In 10 of the 11 errors, cycloserine was placed as a historical medication, so no new prescription was generated. In one case, cycloserine was ordered in error, and a prescription was generated for the patient in the ambulatory setting. The patient was already on cyclosporine for aplastic anemia. The patient received cycloserine for four months but there was no notation in the medical record as to what prompted the discontinuation of cycloserine after four months or whether the patient experienced any adverse events during this time period. The patient appeared to be taking cyclosporine at least near the end of the time period as evidenced by a therapeutic level documented roughly 4 months after the cycloserine prescription.

Publications

Rash-Foanio, C., Galanter, W., Bryson, M., Falck, S., Liu, K. L., Schiff, G. D., . . . Lambert, B. L. (2017). Automated detection of look-alike/sound-alike medication errors. *American Journal of Health-System Pharmacy*, 74(7), 521-527. doi:10.2146/ajhp150690

Study 2: Full Scale Evaluation on One Year of Medication Orders at UIC

Purpose

The purpose of this study is to assess the positive predictive value of our algorithm for detecting wrong drug errors.

Scope

Drug names that look and sound alike are a leading cause of medication errors (e.g., diazepam and diltiazem, hydroxyzine and hydralazine, *Paxil* and *Taxol*, fomepizole and omeprazole, *Foradil* and *Toradol*).⁹⁻¹³ The U.S. Pharmacopeia published a comprehensive review of name confusion errors from two large databases of spontaneous error reports (MEDMARX and IMSP/USP Medication Error Reporting Program) covering the years 2003-2006.¹ They identified 26,604 look-alike/sound-alike errors involving 3,170 confusing

pairs of drug names, 1.4% of which caused patient harm. Observational studies of dispensing in outpatient pharmacies suggest that the rate of wrong drug errors—the type most likely to be the result of name confusion—is roughly 0.13%.⁵ With 3.9 billion prescriptions dispensed in 2009,¹⁴ that translates to 5 million wrong drug errors per year in the U.S. If 6.5% were clinically significant,⁵ that would mean potential harm to roughly 325,000 people annually. Wrong drug errors are the most common source of malpractice claims against pharmacists.¹⁵ Despite advances in technology, policy and practice, and more than a decade of focused effort, preventing drugs with similar names from being confused by clinicians and patients remains an elusive goal.

The two traditional approaches to detecting drug name confusions involve either spontaneous reporting or direct observation of dispensing. Spontaneous reporting is unreliable due to under reporting (and sometimes over reporting) biases. Direct observation is the most valid method but is time consuming, expensive, and does not scale to allow analysis of large numbers of prescriptions. Automated methods of medication error detection have been widely advocated and shown considerable promise.^{16 17} What is needed are methods that approach the reliability and validity of direct observation but are less resource-intensive and hence can scale to millions of prescriptions. Our approach involves computer analysis of electronic medical record data. It looks for suspicious patterns of drugs and diagnoses within the same patient (e.g., “Flomax, Flomax, Flomax, Fosamax” in a male patient with no active diagnosis justifying Fosamax). Automated techniques have several important advantages: (1) they are objective; (2) they exploit the growing presence of electronic medical records; (3) they are generalizable; (4) they can be validated; (5) they are efficient and scalable; and (6) in the future they have the potential for real time application. Others have attempted aspects of this approach. Phatak et al. sought to develop an algorithm to detect potential drug name confusion errors in a database of Idaho Medicaid prescription claims.¹⁸ But they simply scanned for suspicious patterns of known pairs of confusing names. They did not cross reference for justifying diagnoses, and they did no validation by chart review. Basco and colleagues took a small number of existing look-alike/sound-alike name pairs where one was a common pediatric drug and the other a drug used mostly in adults. They screened a Medicaid population of pediatric patients looking for patients who got both drugs and who lacked a justifying diagnosis for the adult drug.¹⁹ They did no chart validation, studied only 22 drugs and were confined to pediatrics. Both studies nonetheless found scores of potential errors.

Our approach breaks new ground in that it does not depend on pairs of previously confused names. Instead, it looks at claims data for any drug that is not justified by an active diagnosis. It then determines whether a look-alike drug exists that does match an active diagnosis. If so, it generates an alert. And our algorithms rely on sophisticated, hybrid measures of similarity, developed during our 15 years of work on in this domain.^{13 20} In another project (5R44RR021232-03) we have developed a rule that ranks the probability of an actual name confusion based on many factors, e.g., the lack of a justifying diagnosis, the similarity of the two names, the relative prescribing frequencies of the names, the relative frequency of the indications for each drug, the frequency with which each drug appears without a matching diagnosis in the overall data set, whether the drug is typically used chronically or acutely, etc. And finally, we did chart review to validate our automated alerts. Together these innovations allowed us to advance the state of the art in valid, automated measurement of drug name confusions using administrative claims or EHR data.

Methods

We extracted one year’s worth of all inpatient and outpatient medication orders from the University of Illinois Hospital and Health Sciences Center (UIH). We selected a subset of those medications, focusing primarily on those that were on the inpatient formulary. We licensed a database of drug indications and spent a year cleaning and improving the data so that we had a validated list of ICD9 indications for every study drug. We ran our algorithm (shown above) on the database, generating a set of alerts. We segmented the alerts based on the similarity between the ordered drug and the drug we suspected was intended to be ordered. Next, we validated the alerts by chart review. Where there were fewer than 100 alerts in a segment, we opened every chart. Where there were more than 100, we randomly selected a subset to review. Each chart was reviewed by two clinicians (two PharmDs and one MD) whose main task was to assess whether a real error had occurred and, if so, what the intended drug was likely to have been. When the two primary reviewers disagreed, a third reviewer adjudicated the disagreement, and the third reviewer’s judgment was taken as final.

There were 3,531,891 orders in our dataset for drugs that were also in our indications dataset. The algorithm only looked at medications that were ordered only once, based on the assumption that these were more likely to be errors. We further restricted the analysis to patients for whom we had diagnosis data from five different days. After applying these criteria there were 556,225 orders remaining.

Results

We ran the algorithm on 556,225 orders and produced 2405 alerts. The results of chart review are given in the table below.

Similarity Levels	Yes cases	Total cases reviewed by Sim Levels	Cases remaining by Sim Levels	Positive Predictive Value by Sim levels
1	3	128	981	2.3%
2	4	100	557	4.0%
3	7	57	281	12.3%
4	1	94	44	1.1%
5	1	31	0	3.2%
6	5	39	0	12.8%
7	5	8	0	62.5%
8	24	38	0	63.2%
9	1	2	0	50%
10	9	9	0	100%
Total	60	506	1863	11.9%

Examples of the types of errors we found are given in the table below.

Sim Level	Ordered	Likely Intended
1	hydrochlorothiazide	hydroxyzine
2	azathioprine	Azithromycin
	escitalopram	enalapril
3	loratadine	lovastatin
	levocetirizine	levothyroxine
	metoprolol	metoclopramide
	nitrofurantoin	nitroglycerin
	tizanidine	ranitidine
	diphenhydramine	desipramine
4	dicyclomine	doxycycline
5	sumatriptan	somatropin
6	lactase	lactulose
	cyclobenzaprine	cyclosporine
	methohexital	methotrexate
7	clomiphene	clomipramine
	rifampin	rifaximin
8	sulfadiazine	sulfasalazine
	hydralazine	hydroxyzine
	valganciclovir	valacyclovir
9	butabarbital	butalbital
10	cycloserine	cyclosporine

Results indicate that the algorithm has a positive predictive value (PPV) of 12% across all levels of similarity, but a much higher PPV at higher similarity levels. The similarity cutoff to use in practice will be tradeoff between the effort available to screen alerts and the desire to detect all possible errors.

Publications

Manuscript is in preparation.

3.B.3. Aim 3. Evaluate Effectiveness of CPOE Indication Prompts

Purpose and Scope

The purpose of these projects was to investigate whether clinical decision alerts given at the point of prescribing could increase the accuracy of the problem list while reducing the rate of wrong drug and wrong patient errors. So-called indication alerts warn a prescriber that the drug being ordered does not correspond to any problem on the patient's problem list.

Results.

We have published two manuscripts on this Aim, and work on it is now complete. We continue to work on the idea of indications based prescribing using non-CERT AHRQ funds awarded to Dr. Gordon Schiff for a study of the feasibility of implementing indications-based prescribing on a national scale. We also obtained two additional AHRQ grants to further develop our work on in this area.

Publications

Galanter W, Falck S, Burns M, Laragh M, Lambert BL. Indication-based prescribing prevents wrong-patient medication errors in computerized provider order entry (CPOE). *Journal of the American Medical Informatics Association : JAMIA*. May 1 2013;20(3):477-481.

Galanter WL, Bryson ML, Falck S, et al. Indication alerts intercept drug name confusion errors during computerized entry of medication orders. *PloS one*. 2014;9(7):e101977.

Grants

1R01HS024945-01 AHRQ	Lambert (PI)	9/30/16-9/29/21
Goal is to improve patient safety and the quality of care by developing and testing a large set of alerts and demonstrating, at two large health systems, that alerts can help prevent wrong-drug and wrong-patient errors and improve the completeness of the problem list. Role: PI		
1R01HS023694-01 AHRQ	Schiff (PI)	9/30/14-9/29/17
Enhancing medication CPOE safety and quality by indications-based prescribing Goal is to facilitate the adoption and implementation of policies and technologies that will promote the inclusion of indication information on all prescription medication orders. Role: Consultant		

Project Area 4. A Primary Care, EHR-Based Strategy to Promote Safe and Appropriate Drug Use

Purpose

The aims of this study have not been modified since the original approval. Below are the aims as they were stated in the original grant application:

1. Refine and field test an EHR strategy for generating and distributing low literacy prescription information for English and Spanish-speaking patients
2. Assess the process of the EHR intervention and its fidelity for providing prescription information for patients at the point of prescribing and dispensing medications.
3. Evaluate the effectiveness of the EHR strategy to improve medication understanding, reconciliation, regimen consolidation, and adherence compared to standard care.

The overall objective of this study was to evaluate a health literacy-informed, electronic health record-based strategy for promoting safe and effective prescription medication use in a primary care setting.

Scope

According to the Institute of Medicine, more than 1.5 million preventable drug events occur each year in the USA. A third of these occur in outpatient settings, at a cost of approximately \$4.2 billion annually. Ensuring safe medication use is likely to become increasingly important as the number of adults taking prescription medications has risen dramatically. Nearly half of Americans take at least one prescription medication, and one in ten takes five or more drugs, an increase of 70% since 1999. Despite frequent use, many adults struggle to take medications, with estimates indicating that only half of adults take drugs as prescribed. Medication use may be particularly challenging for diabetic patients, who must often manage multiple comorbidities and complex multidrug regimens. Patients with low health literacy and limited English proficiency are likely to experience even greater confusion and negative medication-related outcomes, emphasizing the need for innovative and effective strategies to promote positive medication-related outcomes in this vulnerable population. To address these challenges, we designed a health literacy-informed, electronic health record based strategy for promoting safe and effective prescription medication use among English and Spanish-speaking patients with diabetes mellitus.

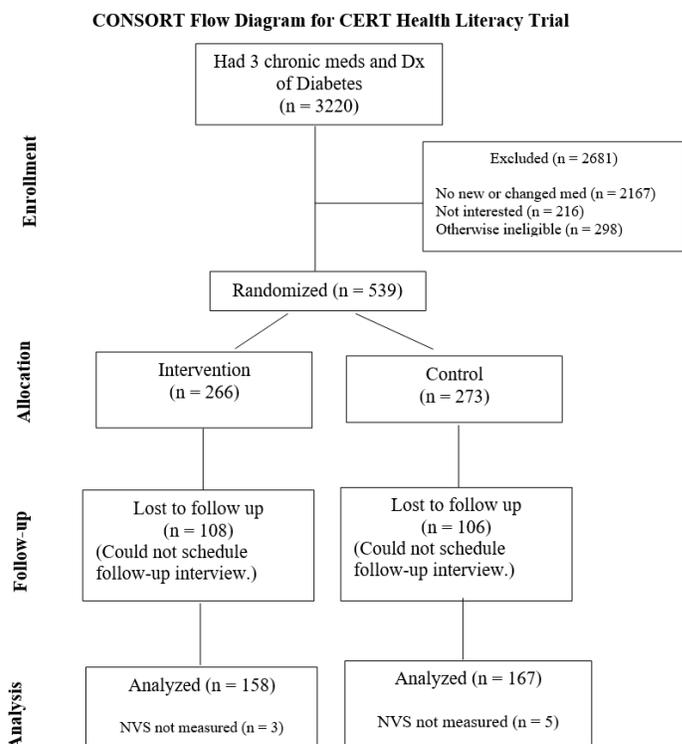
We hypothesize that in comparison with patients receiving standard care, the patients that received the EHR strategy will 1) demonstrate better understanding of how to safely dose out their medication regimen; 2) have fewer discrepancies in their medication lists; 3) take their medication regimen more efficiently; 4) have greater adherence to their medication regimen. In addition, we will be powered to also investigate our strategy's impact on intermediary clinical outcomes including systolic blood pressure, HbA1c, and LDL cholesterol.

Methods

A total of 539 English and Spanish-speaking patients with diabetes were consecutively recruited to participate in the study. Patients were randomized to receive either usual care or the intervention; those in the intervention arm received a set of print materials designed to support medication use and prompt provider counseling and medication reconciliation. Participants were interviewed in person after their index clinic visit and again one month later. Process outcomes related to intervention delivery were recorded. A medical chart review was performed at 6 months. Patient outcome measures included medication understanding, adherence and clinical measures (hemoglobin A1c, blood pressure, and cholesterol; exploratory outcomes only).

Results

The CONSORT diagram for the trial is below.



Final analyses are still underway, but preliminary analyses revealed null results for most outcomes.

Publications

Wolf, M. S., Pryztula, K., Bailey, S. C., Galanter, W. L., Lambert, B. L., Shrestha, N., Dickens, C., Falck, S. A. *Primary Care, EHR-Based Strategy to Promote Safe and Appropriate Drug Use*. *Trials*. 2015 Jan 27; 16(1):17.

Additional Miscellaneous Publications

Dickens, C., Lambert, B., Cromwell, T., & Piano, M. (2013). Nurse overestimation of patients' health literacy. *Journal of Health Communication, 18(sup1), 62-69*.

Lambert, B. L., Schroeder, S. R., & Galanter, W. L. (2015). Does Tall Man lettering prevent drug name confusion errors? Incomplete and contradictory evidence suggests need for definitive study. *BMJ Quality & Safety*. doi: 10.1136/bmjqs-2015-004929.

McMullen CK, Safford MM, Bosworth HB, Phansalkar S, Leong A, Fagan MB, Trontell A, Rumptz M, Vandermeer ML, The Centers for Education and Research on Therapeutics (CERTs) Patient-Centered Medication Management (PCMM) Workshop Working Group. (2015). Patient-centered priorities for improving medication management and adherence. *Patient Educ Couns.* (98): 102-110.

Qato, D., Lambert, B. L., Daviglus, M., & Lee, T. A. (2014). 'Pharmacy deserts' are prevalent in Chicago's predominantly black communities, raising concerns about access to medications. *Health Affairs, 33(11), 1958-1965*.

Quist, A. J., Hickman, T. T., Amato, M. G., Volk, L. A., Salazar, A., Robertson, A., Wright, A., Bates, D. W., Phansalkar, S., Lambert, B. L., & Schiff, G. D. (2017). Analysis of variations in the display of drug names in computerized prescriber-order-entry systems. *American Journal of Health-System Pharmacy, 74(7), 499-509*. doi:10.2146/ajhp151051

Slight S., Berner, E., Galanter, B., Huff, S., Lambert, B., Lannon, C., Lehmann, C., McCourt, B., McNamara, M., Menachemi, N., Payne, T., Spooner, A., Schiff, G., Wang, T., Akincigil, A., Crystal S., Fortmann, S., Vandermeer, M., Bates, D. Meaningful Use: Experiences from the Field and Future Opportunities. (revise and resubmit). *Journal of Medical Internet Research*

- Walton, S. M., Rash, C., Lambert, B. L., & Galanter, W. L. (2014). A case study in generic drug use: Should there be risk adjustment in incentive payments for the use of generic medications? *Journal of Managed Care and Specialty Pharmacy*, 20(11), 1093-1099.
- Wolf, M. S., Lambert, B. L., Hickner, J. (2016). Promoting health literacy to prevent hospital readmissions: Necessary but not sufficient. *Journal of General Internal Medicine*, 31(5), 455-457. doi: 10.1007/s11606-016-3658-6
- Wolf, M. S., Bailey, S. C., Serper, M., Smith, M., Davis, T. C., Russell, A. L., . . . Lambert, B. (2014). Comparative effectiveness of patient-centered strategies to improve FDA medication guides. *Medical Care*, 52(9), 781-789. doi:10.1097/MLR.000000000000182

E.1.2. Non Refereed

Health Literacy Blog Entry Emmi Solutions website: <http://engagingthepatient.com/2014/10/17/fragmentation-complexity-and-the-consequences-of-low-healthy-literacy/>

<http://www.npsf.org/updates-news-press/research-news/looking-for-safety-in-numbers/>

<http://www.npsf.org/blogpost/1158873/214481/Intercepting-Drug-Name-Confusion-Errors?hhSearchTerms=%22galanter%22&terms=>

Uploaded Literacy materials onto: <http://www.uic.edu/com/dom/gim/TOPMEDS/ADHERENCE/>

Statistics Article published on NPSF website (Looking for Safety in Numbers): http://www.npsf.org/?CERT_statistics

F. Project Generated Resources

The DrugStat statistical software: <http://www.healthstats.org/drugstat.html>

Low literacy enhanced written drug information on 90 most frequently used medications among patients with type 2 diabetes, along with pre-visit and post-visit medication lists:

<http://www.uic.edu/com/dom/gim/TOPMEDS/ADHERENCE/>

Video instructing residents how to use the opioid dosing simulator:

<https://www.youtube.com/watch?v=0z-ODKUN7y4&feature=youtu.be>

Opioid Dosing Simulator (dosingsim.org)

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