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IMPLEMENTATION OF AN OUTPATIENT ANTIMICROBIAL STEWARDSHIP PROGRAM TO REDUCE FLUOROQUINOLONE OVERPRESCRIBING AT A VETERANS AFFAIRS ACADEMIC MEDICAL CENTER

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Dedication

I dedicate this thesis to Dr. Richard M. Cadle, PharmD, FASHP, BCPS. Dr. Cadle served as a source of support, inspiration, and encouragement during the early stages of my pharmacy residency experience. He enjoyed educating and training pharmacy students and residents, and he had a passion for developing future pharmacy leaders.

Implementation of an Outpatient Antimicrobial Stewardship Program to Reduce Fluoroquinolone Overprescribing at a Veterans Affairs Academic Medical Center

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Abstract

Background: Fluoroquinolones are often overprescribed in outpatient settings, and antibiotic stewardship programs designed to prevent overuse are not well described. The primary purpose of this study was to evaluate the change in overall and appropriate fluoroquinolone prescribing rates by primary care providers at a Veterans Affairs Medical Center before and after implementation of an audit and feedback intervention.

Methods: After a medical chart audit to assess appropriateness of fluoroquinolone prescriptions to outpatient medical teams, feedback was given to providers regarding monthly fluoroquinolone utilization and prescribing patterns along with monthly didactic lectures on appropriate fluoroquinolone use. Study objectives were assessed before and after the intervention time period using segmented regression time series analysis including a non-intervention comparator clinic.

Results: In the non-intervention clinics, rates of fluoroquinolone orders increased from 3.9±5.2 orders per week per 1,000 patient visits in the pre-intervention time period to 5.8±6.7 orders per week per 1,000 patient visits in the post-intervention time periods. In the intervention clinics, rates of fluoroquinolone orders decreased from 9.4±5.8 orders per week per 1,000 patient visits in the pre-intervention time period to 6.9±6.6 orders per week per 1,000 patient visits in the post-intervention time periods. Using segmented regression analysis controlling for change in prescribing rates in the non-intervention clinics and changes in the rate of prescribing over time, the intervention was associated with a 3.1±0.99 decrease in fluoroquinolone orders per week per 1,000 patient visits ($p=0.0019$). The percentage of orders deemed appropriate increased from increased from 50±31% in the pre-intervention time period to 66±53% in the post-intervention time period ($p=0.06$).

Conclusion: An audit and feedback intervention in ambulatory care clinics was able to reduce the rate of fluoroquinolone orders and increase the percent of orders deemed appropriate.

Keywords: Antimicrobial stewardship; prospective audit and feedback

Background

The majority of antimicrobial prescribing in the USA occurs in outpatient care settings and accounts for greater than 60% of all antibiotic expenditures prescribed.[1] Approximately 30% of these orders are deemed inappropriate or unnecessary and are often of broader spectrum than what is needed for first line therapy.[2-5] One particular class of antibiotics, fluoroquinolones are especially prone to overuse due to ease of dosing and multiple indications. However fluoroquinolones are associated with resistance development, serious side effects and several FDA black box warnings. While, fluoroquinolones place in therapy varies based on condition, they are generally now believed to be best utilized as second-line agents.[6] Outpatient antimicrobial stewardship efforts are essential to combat the issues of antibiotic safety and antibiotic resistance. This is especially important within Veterans Affairs (VA) facilities, as older adults constitute a large percentage of the patient population and are prone to adverse consequences of antimicrobial overuse.[6-10] Additionally, analysis of outpatient surveillance data from 2000-2010 demonstrated that fluoroquinolone resistance to *Escherichia coli*, a common pathogen that causes urinary tract infections for which fluoroquinolones are prescribed, increased significantly and faster among patients 65 or older compared to adult patients less than 65 years of age.[7]

Audit and feedback is a commonly used mechanism to support changes in clinical behavior by healthcare professionals. It provides clinical performance summaries to healthcare providers to promote positive change in healthcare practices. The information is obtained from computerized databases, medical records or patient observations.[11] Other interventions used in conjunction with audit and feedback can include patient education, clinician reminders, formulary restriction,

and delayed prescribing. It has been shown that combining multiple interventions can lead to significant changes in prescribing behaviors of providers as opposed to using a single intervention. [12-13] However, in ambulatory care clinics with a diverse set of clinicians, it can be difficult to execute bundled interventions of an antimicrobial stewardship program in ambulatory care clinics with a diverse set of clinicians. As part of an ongoing emphasis by our antimicrobial stewardship leadership team, we sought to begin an Outpatient Antimicrobial Stewardship Program in the ambulatory care clinic setting. The program used our infectious diseases pharmacists and physician champions to deliver peer-to-peer education and our universal electronic health record to gather audit and feedback data. The purpose of this project was to assess weekly fluoroquinolone utilization rates and appropriateness of fluoroquinolone prescribing before and after the start of the Outpatient Antimicrobial Stewardship Program.

Methods

Study Design and Setting

This was an interrupted time series analysis evaluating interventions to decrease the rate of outpatient fluoroquinolone prescribing over time by internal medicine primary care providers and to also increase the percent of appropriate outpatient fluoroquinolone prescribing, deemed appropriate. This study was conducted at the Michael E. DeBakey Veterans Affairs Medical Center, a 538 bed academic medical center affiliated with Baylor College of Medicine in Houston, Texas. The hospital serves as the primary health care provider for almost 130,000 veterans in southeast Texas. The institution contains four internal medicine primary care clinics on site, and nine community based outpatient internal medicine clinics located throughout southeast Texas. The internal medicine primary care clinics located at the institution are known

as Patient Aligned Care Teams (PACTs). Each PACT has six to eight primary care physicians assigned to each primary care clinic for a total of 28 primary care physicians. Three nurse practitioners and three physician assistants are also employed in the clinics. Most patients served within these clinics are older male patients with diverse racial and socioeconomic backgrounds. Among all thirteen clinics, an average of 1,425 patients are seen per month in each clinic.

The study period was from July 2017 until March 2018. The study included three phases: Phase I consisted of a three month pre-intervention phase from July 2017 to September 2017, Phase II was from October 2017 to December 2017, and Phase III was from January 2018-March 2018. Phase II of the study consisted of a lead-in period coupled with one academic detailing session, and the providers were notified that monitoring of fluoroquinolone prescribing patterns would begin. Phase III consisted of monthly face to face academic detailing sessions coupled with audit and feedback of fluoroquinolone prescribing within the four internal medicine primary care clinics on site during their monthly journal club meetings. The primary outcome was the rate in which fluoroquinolones were prescribed before and after the start of the intervention. The secondary outcome was the change in the appropriateness of prescribing before and after implementation. The rate of prescribing in the four intervention clinics was compared to four VA community based outpatient clinics that were similar in terms of patient characteristics, number of providers per clinic, and patient panel size. All fluoroquinolone prescriptions written by a primary care provider in both the intervention and non-intervention clinics that were filled at a Veterans Affairs pharmacy were included in this study. This study was approved by the Committee for the Protection of Research Subjects at the University of Houston and the Research and Development Department at the Michael E. DeBakey Veterans Affairs Medical Center (MEDVAMC).

Data Collection and Study Definitions

Data on fluoroquinolone usage was obtained from the Veterans Integrated Services Network (VISN) 16 and the Computerized Patient Record System (CPRS). Monthly fluoroquinolone utilization data within all internal medicine clinics affiliated with the MEDVAMC was received from VISN 16. Information received in the data set included the total number of fluoroquinolones prescribed per month per clinic per provider, date the prescriptions were written, quantity, dose, day supply, and the practice site where the prescription was prescribed. Patient and clinic visit level data including age, sex, date of clinic visit, diagnosis, and clinician type (physician, nurse practitioner, physician assistant) was obtained from CPRS. The issue date of the fluoroquinolone prescription was matched to the clinic visit date and the infection diagnosis documented by the provider. To assess appropriateness of fluoroquinolone prescribing, a pharmacist reviewed fluoroquinolone prescriptions using the electronic health record. A prescription was defined as appropriate if it was written for an appropriate diagnosis, correct dose, and correct duration of therapy based on the VA empiric antibiotic recommendations guideline (Table 1). [14] The VA empiric antibiotic guidelines are based on guidelines published by the Infectious Disease Society of America, our hospital-specific antibiogram and recommendations from our infectious diseases physicians and pharmacists. Infectious Disease pharmacists and physicians were available for consultation on cases where the primary reviewer needed assistance in classifying fluoroquinolone appropriateness.

Intervention

The intervention consisted of two phases. In phase II, the study team met with the primary care providers face to face to provide academic detailing sessions. The sessions consisted of

reviewing project goals, providing baseline fluoroquinolone utilization data, providing education on the Food and Drug Administration black box warning regarding fluoroquinolones, and reviewing the institution's empiric antibiotic treatment guidelines and antibiogram.[6] Disease state education was provided to the group over the next two months to complete phase II. In phase III, audit and feedback data was provided to each provider each month with continuation of the monthly academic detailing sessions. All academic detailing sessions entailed 30 minutes of disease state education. In January 2018, education was provided on the treatment of skin and soft tissue infections, asymptomatic bacteriuria, and lower respiratory tract infections. The providers were educated on the treatment of urinary tract infections in February 2018. A 30-minute aggregate summary of the audit and feedback results for the month prior was presented after each academic detailing session. One-on-one provider education was also provided, if requested.

Statistical Analysis

Study objectives were assessed throughout the study period using segmented regression time series analysis, which included non-intervention comparator clinics using data from July 2016 to March 2018. To assess changes in fluoroquinolone orders before and after the intervention, weekly prescribing rates were compared using linear multivariate segmented regression analysis. To assess for other influencing factors, rates of prescribing from similar, non-intervention clinics were used as a comparator group in the analysis. Separate analyses were performed for moxifloxacin and levofloxacin combined. They were separated from ciprofloxacin due to the differing indications and usage of those fluoroquinolones. To assess for appropriateness of fluoroquinolone prescribing, proportion of orders deemed appropriate before and after the

intervention was assessed using a paired t-test. SPSS statistical software v24 or SAS v9.3 (SAS Institute, Cary NC) was used for all analyses. A $p<0.05$ was considered significant.

Results

A total of 199,074 patients were seen in the intervention and non-interventions clinics during the study time period. The total number of antimicrobial orders and fluoroquinolone orders prescribed during the study time period is displayed in table two. In the non-intervention clinics, rates of fluoroquinolone orders increased from 3.9±5.2 orders per week per 1,000 patient visits in the pre-intervention time period to 5.8±6.7 orders per week per 1,000 patient visits in the post-intervention time periods. In the intervention clinics, rates of fluoroquinolone orders decreased from 9.4±5.8 orders per week per 1,000 patient visits in the pre-intervention time period to 6.9±6.6 orders per week per 1,000 patient visits in the post-intervention time periods (Figure 1). Using segmented regression analysis controlling for change in rates in the non-intervention clinics and changes in rate over time, the intervention was associated with a 3.1±0.99 decrease in fluoroquinolone orders per week per 1,000 patient visits ($p=0.0019$). In intervention clinics, appropriateness of fluoroquinolone orders increased from 50±31% in the pre-intervention time period to 66±53% in the post-intervention time period ($p=0.06$).

Discussion

Overprescribing of antimicrobials is a common occurrence in ambulatory care practices. In this study, we designed an audit and feedback intervention in conjunction with active education to design a program to reduce fluoroquinolone prescribing among multiple ambulatory care clinics. Using a quasi-experimental study we demonstrated reduced fluoroquinolone orders and an

increased proportion of appropriate fluoroquinolone orders that were deemed appropriate. Other studies have shown improved antibiotic prescribing in primary care through a variety of interventions.[14-16] A cluster randomized trial conducted by Juzych, N. S., et al. implemented three interventions alone or in combination to attempt to change prescribing behaviors of primary care providers. Their study was similar to ours in that it consisted of a multi-faceted approach to change prescribing patterns, but the format differed from our study. The first intervention consisted of utilizing order sets to encourage providers to use non-antibiotic alternative therapies. Secondly, providers were prompted to provide free-text justification when prescribing antibiotics. Lastly, providers were sent e-mails that compared their antibiotic prescribing rates with other providers. The study found that peer comparison and accountable justification reduced inappropriate antibiotic prescribing for acute respiratory infections.[15] Outpatient antimicrobial stewardship programs targeting upper respiratory tract infections have also used a multi-faceted approach to decreasing antibiotic prescribing (Table 3). [16-18] Other studies have evaluated the impact of prospective audit and feedback interventions on antibiotic prescribing within a single department. A controlled interrupted time series study by Tavares, M., et al. was conducted using an audit and feedback intervention to reduce the use of fluoroquinolones and carbapenems and decrease antimicrobial resistance within an orthopedics department. Prescriptions were audited twice weekly targeting specific antibiotics, and feedback was provided via telephone or within the electronic health record. The feedback provided was similar to our study in that it was comprised of recommendations for duration of therapy and dosages of medication. Due to the fact that the study setting was within an orthopedics department, feedback was also provided in regard to the conversion of intravenous antibiotics to oral antibiotics, use of narrow or broad-spectrum antibiotics, and source control. The study

evaluated the change in fluoroquinolone use compared to the General Surgery department, and the intervention led to a decrease in the use of fluoroquinolones by 2.3 doses per day per 1000 patient days. [19]

Our study had some limitations. We cannot determine which intervention, (education, audit and feedback), drove the decrease in fluoroquinolone prescribing rates. The rate of prescribing may have also decreased due to provider awareness regarding auditing of prescriptions. We did not evaluate and compare the appropriateness of fluoroquinolone prescribing from July 2016 to March 2017 compared to July 2017 to March 2018. Additionally, the sustainability of our interventions after the conclusion of the study cannot be accurately assessed. Other studies that have used audit and feedback interventions to promote antimicrobial stewardship have not been able to sustain improvements in prescribing behavior of providers. This has demonstrated that continued efforts and interventions are required to maintain improvements in antibiotic prescribing.[20-21]

This study demonstrated that audit and feedback interventions coupled with provider education can change prescribing patterns of providers and the utilization of fluoroquinolones improved. The goal of Antimicrobial Stewardship Programs is to decrease antimicrobial resistance, which is associated with increased mortality and increased cost. This study serves as the first of its kind to assess fluoroquinolone utilization within a Veteran population in the primary care setting as it relates to appropriateness of prescribing and using targeted interventions to improve appropriate prescribing.

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Definitions of Appropriateness	
Appropriate Diagnosis	Use of a fluoroquinolone for a diagnosis for which a fluoroquinolone is indicated in the correct line of therapy (i.e. used as second-line agent due to a valid reason for non-use of the first line agent)
Correct Dose	Correct dose for the diagnosis based on VA guidelines appropriately adjusted for the patient's renal function
Duration of Therapy	Correct duration of therapy based on VA guidelines and standard practice for the disease being treated

Table 1. Definitions of Appropriateness

	Patient Visits	**Antimicrobial orders**	**Antimicrobial orders/1000 patient visits**	**Number of fluoroquinolone orders**	**Number of fluoroquinolone orders/1000 patient visits**
Intervention Clinics	103,786	5,044	48.6	850	8.2
Non-Intervention Clinics	95,288	2,362	24.8	400	4.2
Totals	199,074	7,406	37.2	1250	6.3

Table 2. Prescription and clinic visit data

Study Type	Interventions	Setting	Primary Outcome	Results
Cluster-randomized controlled trial	• Clinician guidelines • Caregiver education • Peer-review meetings • Clinician education	Rural pediatric primary care facilities in China	Antibiotic prescribing rate in children with upper respiratory tract infections	• Between the intervention and control groups there was a 29% absolute reduction in antibiotic prescribing (p=0.0002)
Prospective non-comparative cohort study	• Clinician education • Audit and feedback • One on one academic detailing • Peer comparison • Diagnostic testing	Pediatric primary care clinic in Dhahran, Saudi Arabia	Antibiotic prescribing rates in children with upper respiratory tract infections	• The monthly rate of inappropriate antibiotic prescribing decreased from 12.3% per month to 3.8% per month during the study time period (p<0.0001)
Prospective, non-randomized controlled trial	• Case and guideline based clinician education targeting prescribing for upper respiratory tract infections	Adult and pediatric primary care clinics in Detroit, Michigan	Antibiotic prescribing rates in adults and children with acute upper respiratory tract infections	• Antibiotic prescribing among adult internal medicine physicians and pediatricians in the intervention group decreased by 24.6% from baseline (p=<0.0001)

Table 3. Interventions to improve antibiotic prescribing for upper respiratory tract infections in the primary care setting

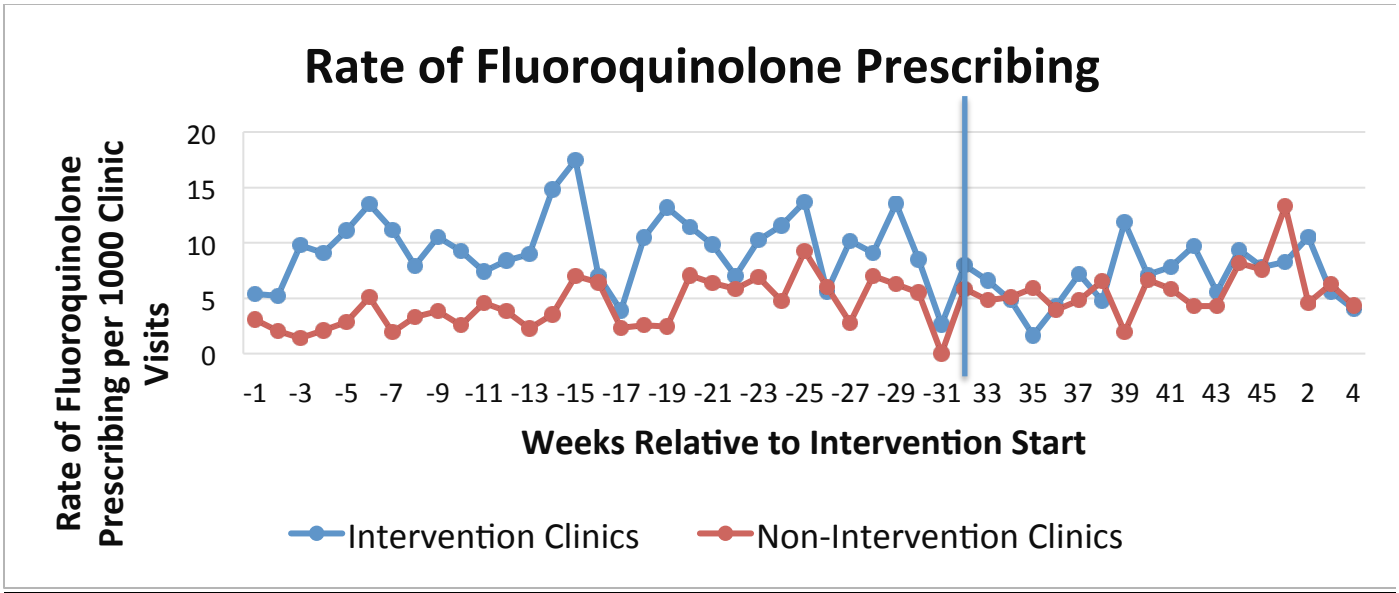

Figure 1. Adjusted rates of fluoroquinolone prescribing