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Cross-Sectional Study Examining the Differences between US Rural and Non-Rural Adults in Appropriate Prescriptions for Nitrofurantoin for the Treatment of Urinary Tract Infections (UTIs) in the ED

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ABSTRACT

Nitrofurantoin is an antibiotic specifically indicated for lower urinary tract infections (UTIs).Rural US populations experience more health care disparities than other groups. Hence, this study sought to answer the question: Are there differences in the appropriate prescribing patterns for nitrofurantoin for the treatment of UTIs in the Emergency Department (ED) between US rural and non-rural adults?**.** Bivariate and multivariate techniques were used to examine2009 National Hospital Ambulatory Medical Care Survey (NHAMCS) data. The study population was US adults presenting to the ED and given a prescription for nitrofurantoin. Appropriate prescribing was determined by ICD-9 codes consistent with lower UTI diagnoses. Bivariate analysis revealed that rural in comparison to non-rural patients were more likely to be prescribed nitrofurantoin for something other than a UTI (OR= 1.393: 95% CI 1.374-1.412). Logistic regression analysis confirmed that rural patients seen in an ED were less likely to have nitrofurantoin appropriately prescribed. When nitrofurantoin was ordered, inappropriate prescribing occurred in nearly 1 in 4 ED encounters. This can lead to treatment failure and significant toxicities. Pharmacists can play a role in ensuring the proper prescribing of nitrofurantoin as well as other medications.

Keywords: NHAMCS data, ED visits for UTI, appropriate nitrofurantoin prescribing, rural health care disparities

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INTRODUCTION

Urinary tract infections (UTIs) are one of the most common infections encountered in emergency departments (ED) and urgent care clinics across the country [1]. Infections can be classified as a lower UTI (urethritis, cystitis) or an upper UTI (pyelonephritis) [2]. According to the 2010 Infectious Disease Society of America (IDSA) guidelines, first-line treatment for uncomplicated lower UTIs include: nitrofurantoin, trimethoprim-sulfamethoxazole (TMP-SMX), fluoroquinolones, fosfomycin, andcertain β-lactams [3]. For treatment of upper UTIs, nitrofurantoin is excluded from the list of first-line medications [3].

The effectiveness of nitrofurantoin for systemic infections is limited by its pharmacokinetics [4]. Although oral nitrofurantoin leads to serum concentration levels above the minimum inhibitory concentration (MIC) of 32 mcg/mL, there is minimal tissue distribution making it unsuitable for treatment of systemic infections [5, 7]. Therefore, when nitrofurantoin is prescribed for an infection other than a lower UTI, treatment failure and development of drug resistance may occur.

Another important pharmacokinetic parameter is a patient's creatinine clearance (CrCl). Nitrofurantoin is rapidly cleared by the kidneys and concentrates in the bladder [4]. This unique property limits its use to the treatment of lower UTIs. Many patients have diminished kidney function and are unable to concentrate the drug properly in the bladder [6]. Furthermore, decreased kidney function puts patients at higher risk of toxicity due to impaired excretion of the medication [7]. For these reasons, nitrofurantoin is contraindicated in patients with a CrCl< 60 ml/min [7]. Because kidney function declines with age, elderly adults are at higher risk of adverse drug reactions when using nitrofurantoin [8].

Due to increased use of broad spectrum antibiotics, many strains of gram negative rods associated with UTIs have developed resistance to first-line therapies including TMP-SMZ and fluoroquinolones[9]. Unlike other antibiotic choices, nitrofurantoin has a unique niche in that it is only indicated for the treatment of lower UTIs [7]. Therefore, the risk of antibiotic exposure leading to resistance should be minimized with the use of nitrofurantoin. For this reason, IDSA guidelines recommend against routinely using fluoroquinolones as a first-line therapy because of *collateral damage* such as systemic drug resistance [3].

Taur and Smith (2007) demonstrated that physician prescribing does not always follow IDSA guidelines for treating UTIs [10]. It is also known that health care disparities exist between rural and non-rural Americans [11]. In fact, a recent paper argued that rurality is an independent risk factor for health disparities [11]. This paper averred that rurality is one of the social determinates of health [11].What is not known, however, is if prescribing patterns exist due to such disparities? The combination of prescribing patterns not always following guidelines and the impact of rurality gives rise to this study that sought to answer the question: Are there differences in the appropriate prescribing patterns of nitrofurantoin for the treatment of UTIs in the ED between US rural and non-rural adults?

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METHODS

To answer the research question, 2009 National Hospital Ambulatory Medical Care Survey (NHAMCS) data were examined using bivariate and multivariate techniques. NHAMCS is designed to collect data on the utilization and provision of ambulatory care services in hospital EDs. Data are collected from a national sample of ED visits. A complex four-stage probability sampling design was used. A description of the sampling strategy is discussed elsewhere [12]. 2009 NHAMCS data were used for this study because it was the most recent data available.

The survey instrument is the *Patient Record* form. ED staff is instructed to complete *Patient Record* forms for a systematic random sample of patient visits during a randomly assigned 4-week reporting period. Data are obtained on demographic characteristics of patients, expected source(s) of payment, patients' complaints, diagnoses, diagnostic/screening services, procedures, medication therapy, disposition, types of providers seen, causes of injury, and certain characteristics of the facility, such as geographic region and metropolitan status.

The study population for this research was US adults 18 to 80 years of age presenting in an ED and prescribed either nitrofurantoin, Macrobid®, or Macrodantin®. The dependent variable for the analyses was appropriate nitrofurantoin prescription based on indication. Appropriate indication was determined by ICD-9 codes (595.0, 595.2, 595.9, 597.8 and 599.0). The codes associated with lower UTI diagnoses include: acute cystitis, chronic cystitis, other cystitis, other urethritis non-sexually transmitted, and UTI non-specific respectively. The following covariates or independent variables for this research were: geographic locale (rural/non-rural), patient sex, race/ethnicity (Caucasian/non-Caucasian), health insurance status (insured/noninsured), education attainment in patient's zip code (<20% of adults with a bachelor's degree/$\geq$ 20% of adults with a bachelor's degree), and median household income in patient's zip code ($\leq$$40,000 median household income/> $40,000 median household income). All of the study covariates were recoded from their original configuration for analyses. Re-coding entailed either collapsing categories and/or removing *unknown* responses.

Bivariate analysis was conducted to establish the relationships between the covariates and prescription for nitrofurantoin. The population of interest was US adults presenting to the emergency department with a UTI diagnosis. Multivariate analysis was performed using appropriate prescription of nitrofurantoin as the dependent variable. Six covariates (patient sex, race and ethnicity, insurance, geographic locale, education attainment in patient's zip code, and median household income in patient's zip code) were entered into the logistic regression model. For all statistical tests alpha was set at <0.05. Statistical Package for Social Scientists (SPSS, IBM, Chicago, version 20.0) was used to conduct the analyses. Human subject approval was sought and received from the Essentia Health Institutional Review Board (IRB).

RESULTS

An analysis of ED diagnosis (UTI vs. non-UTI) by prescription (nitrofurantoin vs. other) yielded that 25.5% of patients receiving a prescription for nitrofurantoin did not have a

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corresponding diagnosis of lower UTI (results not shown). Additional analysis revealed rural adults were more likely than non-rural adults to be prescribed nitrofurantoin for a diagnosis other than a lower UTI (OR= 1.393, 95% CI 1.374-1.412) (results not shown).

Table 1. US ED Patients With Lower UTI Diagnosis by Nitrofurantoin Prescription 2009 NHAMCS Data

Covariates and Factors		Unadjusted Odd Ratio (95% CI)
Median household income in patient's zip code (vs>$40,000)	≤ $40,000	OR= 1.106 (1.100-1.112) Adults with UTI diagnosis living in ZIP codes where mean household income is ≤$40,000 were more likely to be prescribed nitrofurantoin.
Education in patient's ZIP code (vs. >= 20% have bachelor's degree)	< 20% have bachelor's degree	OR=1.508 (1.499-1.517) Adults with UTI diagnosis living in ZIP codes where <20% have a bachelor's degree were more likely have been prescribed nitrofurantoin
Patient Sex (vs. male)	Female	OR= 11.058 (10.843-11.277) Females with UTI diagnosis were more likely to be prescribed nitrofurantoin.
Patient Race/Ethnicity (vs. non-Caucasian)	Caucasian	OR= 0.704 (0.701-0.708) Caucasian adults with UTI diagnosis were less likely to be prescribed nitrofurantoin
Insurance (vs. Do not have health insurance)	Have health insurance	OR= 0.698 (0.694-0.703) Adults with UTI diagnosis who have health insurance were less likely to be prescribed nitrofurantoin.
Geographic Locale (vs. rural)	Non-rural	OR= 1.890 (1.874-1.906) Adults with UTI diagnosis who live in a non-rural area were more likely to be prescribed nitrofurantoin.

Table 1 displays a bivariate analysis conducted to explore the relationships between the covariates and prescription for nitrofurantoin. Notably, this analysis revealed that non-rural in comparison to rural patients were more likely to be prescribed nitrofurantoin for a lower UTI diagnosis (OR=1.890, 95% CI 1.874-1.906).

Table 2. Logistic Regression Model for Characteristics of Patients Receiving Appropriate Nitrofurantoin Prescription for UTI 2009 NHAMCS-ED Data

Covariate	Factor	Adjusted Odds Ratio (95% CI)
Patient Sex	Female	3.645 (3.540, 3.752)
	Male	--*
Patient Race And Ethnicity 2 Categories	Caucasian	1.342 (1.325, 1.359)
	Non-Caucasian	--*
Insurance	Have Health Insurance	2.103 (2.074, 2.132)
	Do Not Have Health Insurance	--*
Geographic Locale	Non-Rural	--*
	Rural	.637 (.626, .649)
Education In Patient's Zip Code	<20% Have Bachelor's Degree	1.258 (1.237, 1.278)
	>=20% Have Bachelor's Degree	--*
Median Household Income In Patient's Zip Code	<=$40,000	1.122 (1.104, 1.140)
	>$40,000	--*

Logistic regression analysis (Table 2) confirmed that rural patients seen in an ED were less likely to have nitrofurantoin appropriately prescribed (OR=0.637, 95% CI 0.626-0.649).

Moreover, this analysis yielded that adults with the following characteristics were more likely to have nitrofurantoin appropriately prescribed: female, Caucasian, and have health insurance.

DISCUSSION

The Food and Drug Administration has only approved nitrofurantoin specifically for the treatment of uncomplicated lower UTIs [7]. However, this study demonstrates that in 25.2% of instances where nitrofurantoin was prescribed there was no corresponding diagnosis of a lower UTI.As mentioned previously, nitrofurantoin is not effective for non-UTI infections because of the drug's lack of tissue distribution [5,7], which implies that at least 25% of nitrofurantoin prescriptions would have potentially resulted in treatment failure.

Nitrofurantoin is not an entirely benign drug. Not only is treatment failure a major concern, but so is patient exposure to an unnecessary drug. A large portion of adverse effects from nitrofurantoin involve gastrointestinal upset or intolerance [13]. Serious adverse events have also been shown including acute/chronic pulmonary disease, allergies, blood dyscrasias, liver damage, and peripheral neuropathy [14]. Again, 25% of patients who received nitrofurantoin were potentially put at risk for developing these adverse events without the outweighing benefit of a successful treatment.

One question arising from the results is: Why is nitrofurantoin being prescribed for non-UTI diagnoses? One plausible theory is based on prescribers' misunderstanding of the drug's pharmacokinetic properties. Pharmacists receive extensive training on pharmacokinetics and can use their skills and knowledge to help educate other health care providers on making correct antibiotic choices. Pharmacist-led antimicrobial stewardship teams have proven better outcomes including antibiotic appropriateness, cure rates, treatment failures, and cost containment [15]. Because pharmacists have shown value in their area of expertise, the IDSA guidelines on antimicrobial stewardship (AMS) have placeda II-A recommendation on ensuring that a clinical pharmacist bea co-lead with an infectious disease physician on an AMS team [16].

In 2007, the American Society of Health-System Pharmacists (ASHP) published their official position on emergency department pharmacists stating that every hospital emergency department should have pharmacists involved in: medication safety, patient care, collaboration and clinical support with physicians and other staff, quality improvement, and education for patients and prescribers on safe and effective medication use [17].Despite the ASHP's official position, a 2009 ASHP survey of US hospital pharmacy departments revealed that only 28.6% of all hospitals have at least 8 hours per day of pharmacist time devoted to the emergency department [18]. A majority of these hospitals were larger institutions, likely in metropolitan areas. Over 50% of hospitals with greater than 300 beds, and over 70% of hospitals with greater than 600 beds, were able to provide such services [18]. This is contrasted with smaller hospitals, such as those found in rural areas, where only 16-30% of pharmacy departments were able to actively be present in the emergency department [18].

Pharmacists play an important role in appropriate antibiotic use. This coupled with the fact that most rural hospitals are smaller in size and have less pharmacy presence in the emergency department, our results indicating that nitrofurantoin was prescribed inappropriately more often in rural areas are not surprising. This supports the position that pharmacists are crucial health care providers needed in rural hospital emergency departments.

LIMITATIONS

This study does have some limitations, many of which are attributable to how the survey data was collected. Nitrofurantoin appropriateness was determined by the presence of an ICD-9 code consistent with an uncomplicated lower UTI. Because there is no link in the questionnaire form between medication and diagnosis, we were unable to determine what diagnosis nitrofurantoin was being used for. There are also several different patient specific variables that would make nitrofurantoin use inappropriate including: patient's kidney function, urinalysis, urine culture and sensitivities, local susceptibility patterns, allergies and previous antibiotic use. We were unable to extract these parameters from the database; however, one would expect an increased number of inappropriate cases if we were able to capture this data.

Nevertheless, this study has a number of strengths. Since we used national hospital survey data, we had a large sample size. With a large sample size generalizable statements about the US population as a whole are more easily made. Another strength is the magnitude of difference between rural and non-rural prescribing patterns, with the logistic regression model showing that rural adults were less likely to receive appropriate nitrofurantoin therapy (OR=0.673, 95%CI 0.626-0.649). This finding contributes to the epidemiological knowledge base regarding health care disparities of rural residents in the United States.

CONCLUSIONS

In conclusion, overall, nitrofurantoin was prescribed inappropriately in at least 25% of cases, based solely on indication. A disproportionate amount of this inappropriate prescribing occured in rural areas. Rural hospital pharmacists, as medication experts, need to be more involved in clinical emergency medicine services to ensure safe and effective medication use.

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