IS NITROFURANTOIN USE REALLY DANGEROUS FOR OLDER ADULTS? A DEEPER DIVE INTO BEERS CRITERIA

By

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DISSERTATION

Presented to the Faculty of the Medical School

The University of Texas Southwestern Medical Center

In Partial Fulfillment of the Requirements

For the Degree of

DOCTOR OF MEDICINE WITH DISTINCTION IN QUALITY IMPROVEMENT

The University of Texas Southwestern Medical Center

Dallas, TX

ACKNOWLEDGEMENTS

This project could have not been possible without the vision, support, and encouragement of my exceptional mentors: Drs. Rubin, Fish, and Reed. Thank you for sharing your passion for medical education, career development, and drive to continually improve medical care. These are skills I will use the rest of my career, so I am forever grateful for the wonderful foundation you all have laid.

This research was supported by Grant T35AG038048 from the National Institute on Aging and the Geriatric Research and Training Fund at University of Texas Southwestern Medical School.

ABSTRACT

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Background: The use of nitrofurantoin (NF) has been quite controversial over the past several years. The Infectious Disease Society of America (IDSA) recommends NF as a first choice treatment for uncomplicated urinary tract infections (UTI's); yet, several quality indicators, specifically the Beers Criteria, include NF as a potentially inappropriate medication (PIM) for adults 65 and older due to a number of concerns, especially pulmonary and hepatic complications. However, many physicians and pharmacists question the Beers Criteria recommendation and believe the adverse event (AE) incidence is low enough to warrant using this antibiotic in the older population.

Objective: We sought to identify the pulmonary and hepatic adverse event rate associated with NF use in a cohort of patients 65 and older to determine if a restriction of the use of NF is needed.

Methods: A retrospective chart audit of patients 65 and older prescribed NF from January 1, 2010, to December 31, 2014 at an urban academic medical center was conducted. Additional inclusion criteria were diagnoses of dyspnea, pulmonary fibrosis, hepatotoxicity, cholestatic jaundice, and chronic hepatitis as documented in the patients' medical records. Two independent reviewers of the medical records assigned patients with the following categories: No Reaction, Allergy, Minor Side Effect, High Suspicion for AE, or Possible Suspicion for AE (A, B or C). If discordance occurred between the two reviewers, a third reviewer provided an additional review assigning the category based on the majority.

Results: Of 3,400 individuals aged 65 and older prescribed nitrofurantoin during the study period, 641 were identified as possibly having one of five targeted symptoms or disease complications (pulmonary and hepatic) associated with nitrofurantoin. After a detailed chart audit, 89% were deemed to have no adverse reaction, 7% had a minor side effect or allergy, and 3.9% (25 patients) met criteria for suspicion of a nitrofurantoin-induced AE, five of whom (0.8%) were rated as highly suspicious for nitrofurantoin toxicity; four of the five were identified

with pulmonary toxicity and one with hepatotoxicity. Four of five of these individuals used nitrofurantoin chronically.

Conclusion: Nitrofurantoin was prescribed for 3,400 individuals aged 65 and older during the 5-year study period. We found a low rate of nitrofurantoin-associated AEs. However, a judicious approach appears warranted with chronic use and in patients for whom toxicity could exacerbate underlying medical conditions (e.g. underlying interstitial disease). Avoiding NF in patients based on age alone should not be seen as a negative quality indicator based on our results. Through patient education and informed prescribers, NF can be used safely in most patients 65 and older.

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Introduction

Nitrofurantoin use in older adults has been controversial. Nitrofurantoin prescriptions have dramatically risen since guideline changes by the Infectious Disease Society of America (IDSA) recommended nitrofurantoin as first-choice treatment for acute uncomplicated cystitis and pyelonephritis in 2011 in premenopausal women.[1] Although the report noted that urinary tract infections (UTIs) in postmenopausal women without urological abnormalities or those with well-controlled diabetes mellitus could be considered to have uncomplicated UTIs, the committee specifically noted that these individuals were outside the scope of the ISDA guidelines. For premenopausal women, the ISDA concluded that nitrofurantoin was the recommended choice because of minimal bacterial resistance, lower propensity for development of drug-resistant organisms, and the drug's effectiveness, which is comparable to three days of trimethoprim with sulfamethoxazole.[1]

Nitrofurantoin remains listed as a potentially inappropriate medication for older adults in the American Geriatrics Society (AGS) Beers Criteria.[2] It was first added to the Beers list in 2002, when the panel of experts wrote that there was "potential for renal impairment and safer alternatives available" and assigned a severity rating of high.[3] In a 2012 Beers update, the rationale for listing included potential for pulmonary toxicity and lack of efficacy in individuals with creatinine clearance less than 60 mL/min per 1.73 m^2 resulting in adequate drug concentration in urine,[4] but evidence of lack of efficacy in individuals with

creatinine clearance less than 60 mL/min per 1.73 m^2 has been questioned,[5] and the 2015 Beers update has been modified to recommend avoidance when creatinine clearance is less than 30 mL/min per 1.73 m^2.[2] In addition, the committee's rationale for avoiding nitrofurantoin included pulmonary toxicity, hepatotoxicity, and peripheral neuropathy, with particular unease about long-term use while safer alternatives are available.[2] The strength of the recommendation from the AGS Beers expert panel remained strong, but the quality of evidence was downgraded from moderate to low.

Despite moderate to low evidence and guidelines suggesting the avoidance of nitrofurantoin in older adults, a quality gap remains, as there is continued use of nitrofurantoin, an effective medication for treatment of UTIs with minimal bacterial resistance, in the older population by providers who personally experience a low adverse event rate. Two of the most serious nitrofurantoin-associated adverse reactions are pulmonary and hepatic.[6-9] Because of published clinical reports are limited, it was decided to explore through retrospective analysis to determine the frequency of pulmonary and hepatic adverse events (AEs) in individuals aged 65 and older prescribed nitrofurantoin in a large multidisciplinary academic health system. By doing so, it was hoped that a better appreciation would be gained of how often there are serious nitrofurantoin-induced adverse reactions and which patients are at high risk for experiencing a serious adverse reaction to the medication. Ultimately, we aim to inform physician decisions regarding the best use and maximizing safety in older

adults prescribed nitrofurantoin.

Methods

Study Design and Population

All individuals aged 65 and older prescribed nitrofurantoin at University of Texas (UT) Southwestern Medical Center clinics or hospitals (University Hospital, Zale-Lipshy Hospital) from January 1, 2010, to December 31, 2014, were identified from electronic health records (EHRs) (Epic Systems Corporation, Verona, WI). Prescriptions are captured regardless of the site origination (hospital, clinic, home, other) and irrespective of the location of the receiving pharmacy. Most prescriptions are e-prescribed, but telephone and printed prescriptions are also recorded in the system. UT Southwestern is a large, urban medial center with a significant geriatric population.

Prescription of nitrofurantoin associated with International Classification of Diseases, Ninth Revision (ICD-9) codes for dyspnea (786.09), pulmonary fibrosis (515), cholestatic jaundice (782.4), chronic hepatitis (571.40), or hepatotoxicity (575.3) helped identify individuals suspected of serious nitrofurantoin-induced adverse events, who were selected for further direct chart audit. We developed a fishbone diagram to organize possible contributing variables for getting a nitrofurantoin-associated adverse event (Figure 1). The most objective factors on the diagram were electronically extracted for study data including age, sex, number of capsules (<30, ≥30), number of individual

prescriptions per person, allergy to nitrofurantoin, and estimated glomerular filtration rate (eGFR) (<60, ≥60 mL/min per 1.73 m^2).

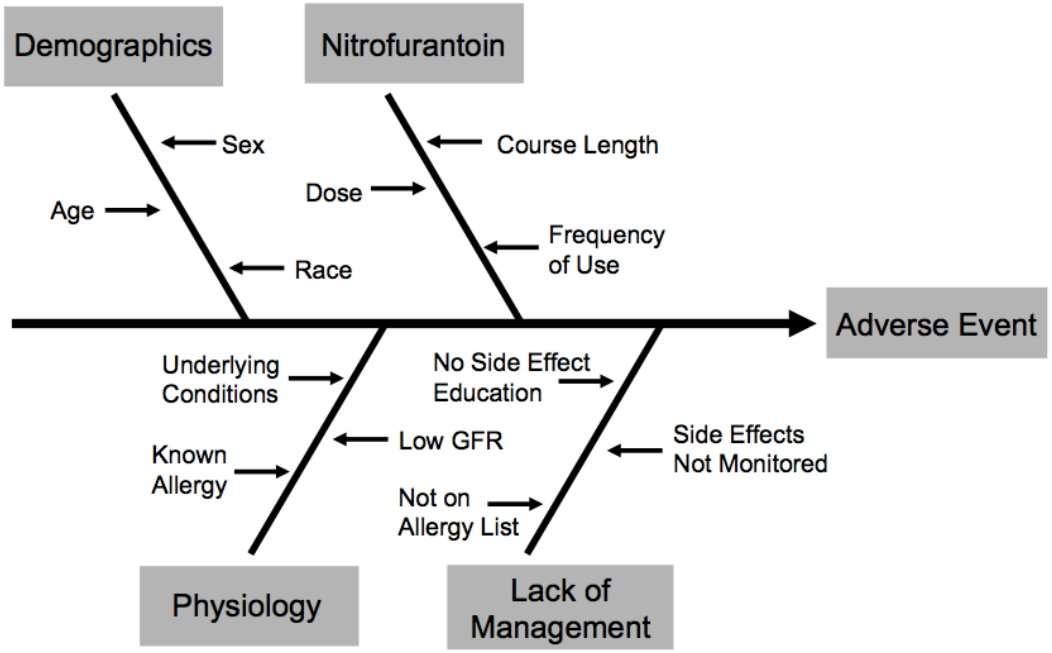

Figure 1. Variables that could contribute to a nitrofurantoin-associated adverse event

Determination of Nitrofurantoin-Associated Adverse Events

Two medical students (myself and a co-medical student) manually audited the EHRs of patients prescribed nitrofurantoin who had one of the suspect diagnostic ICD-9 codes (i.e. dyspnea, pulmonary fibrosis, cholestatic jaundice, chronic hepatitis, or hepatotoxicity) using a decision matrix (Figure 2) to systematically grade the likelihood of a nitrofurantoin-associated AE in order to minimize subjectivity. An adverse event had to occur within six months after episodic prescription (<30 capsules) of nitrofurantoin or within one year after cessation of chronic use (≥30 capsules).

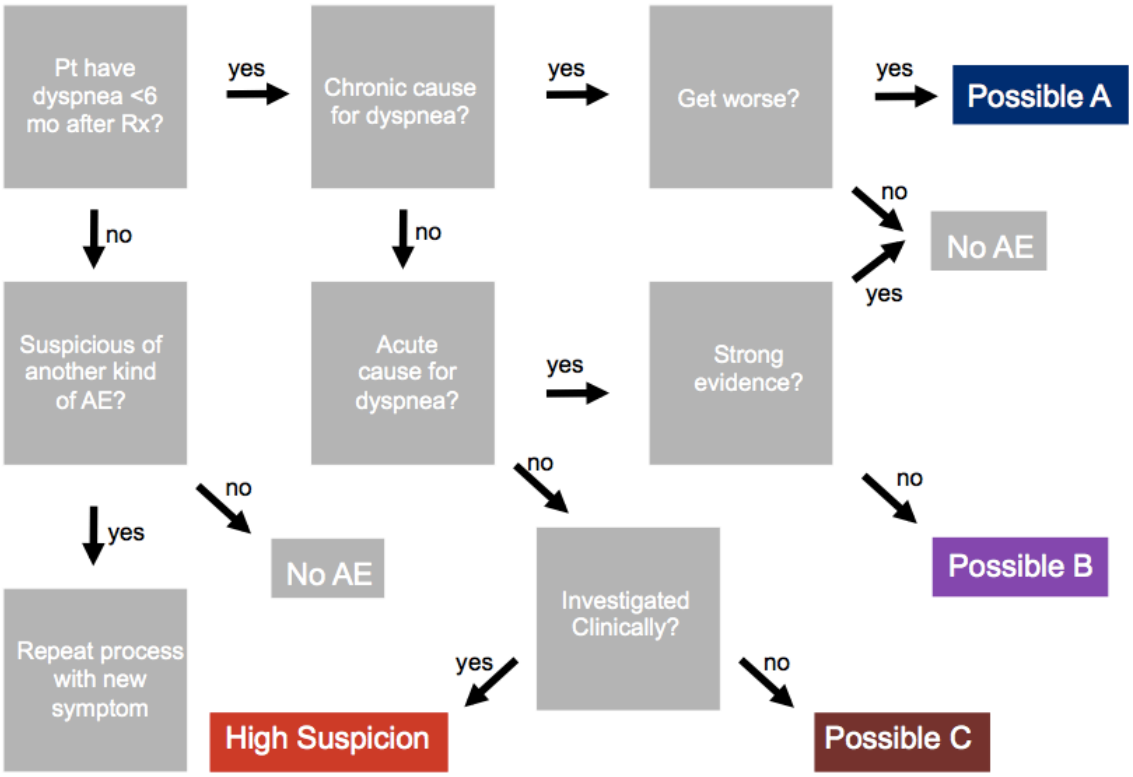

Figure 2. Example Decision Matrix the reviewers used to determine a nitrofurantoin-associated adverse event

The medical record was then inspected for the onset or worsening of the ICD9 code within a certain time period after the ingestion of nitrofurantoin as described above. It was ruled as no adverse event if there were no symptoms or worsening of an underlying disease after ingestion. Additionally, the records were inspected for acute and/or chronic problems that could explain the symptoms, or if their symptoms were consistent with a nitrofurantoin-induced adverse event. The reviewers independently categorized the reaction to the medication or lack thereof into seven categories (Table 1). If discordance occurred between reviewers, a third reviewer, a senior faculty physician (Craig Rubin, MD), examined the chart, and the category was subsequently assigned based on the majority.

Table 1. Nitrofurantoin-Induced Adverse Event (AE) Categories

AE Category	Description
High Suspicion	No relevant underlying conditions, no other cause, highly investigated clinically
Possible A	Possible exacerbation of underlying condition due to nitrofurantoin
Possible B	No relevant underlying conditions, no other causes, evidence not definitive
Possible C	No relevant underlying conditions, no other causes, not investigated clinically
Allergy	Rash, pruritus, swelling, and anaphylaxis
Minor Side Effect	Nausea, diarrhea, and headache
No AE	Nothing in chart indicative on an AE

Individuals classified as high suspicion were determined to have no other underlying condition or acute cause to explain their symptoms after the case was clinically investigated (e.g., chronically taking nitrofurantoin or developed pulmonary fibrosis, all other causes excluded, symptoms improved after cessation of nitrofurantoin).

Possible A individuals had an underlying condition to explain their symptoms (e.g., dyspnea attributed to chronic obstructive pulmonary disease, dyspnea worsened on nitrofurantoin but improved after cessation of nitrofurantoin) and the individual returned to previous baseline after nitrofurantoin cessation. The Possible B cohort had no relevant underlying condition and no

definitive evidence for an acute explanation of their symptoms (e.g., individual in the hospital for dyspnea after taking nitrofurantoin with many possible etiologies for dyspnea; nitrofurantoin as a cause neither confirmed nor excluded). The Possible C cohort consisted of individuals with no underlying conditions or acute cause to explain their symptoms who were not investigated clinically (e.g., patient called during short course of nitrofurantoin reporting transient symptoms and stopped nitrofurantoin).

Nitrofurantoin allergic reactions were noted when pruritus, rash, swelling, or anaphylaxis occurred. Minor adverse reactions were categorized as mild nonspecific for complaints such as nausea, diarrhea, and headache. Charts were excluded if the chart documentation revealed minimal exposure, such as the individual was prescribed three doses or less as suppressive treatment before a urological procedure or lack of documentation of an adverse event.

For individuals with suspected adverse reactions, age, sex, and kidney function (eGFR) were evaluated as contributing factors to nitrofurantoin-associated AEs. Dosage and maximum length of nitrofurantoin therapy were obtained using chart review. Additionally, if a patient was classified as having a possible adverse event, side effect, or allergy, it was noted if nitrofurantoin was coded as an allergy in the patient's electronic medical record.

After the initial evaluation and the determination nitrofurantoin-induced AE, those classified as high or possible suspicion (A, B, C) for drug toxicity were assessed using the Naranjo Adverse Drug Reaction Probability Scale. Although

the scale was developed for use in controlled trials and registration studies of new medications but not for retrospective studies,[10] the scoring was used to provide a degree of consistency of the evaluation. Total scores range from 0 to 13. Score from 1 to 4 are interpreted as possible drug reactions, 5 to 8 as probable drug reactions, and 9 to 13 as definite drug reactions. Scores of 0 or less indicate a doubtful adverse drug reaction.

Statistical Methods

This was a descriptive study. However, age comparisons between individuals with and without a nitrofurantoin-induced adverse event were made using the Cochran-Armitage trend test. Additionally, sex comparisons between those with and without a nitrofurantoin-induced adverse event were analyzed via the Fisher exact test.

Results

Of 3,400 individuals aged 65 and older (average age 76.5, range 65–103) prescribed nitrofurantoin during the study period, 641 were initially identified as having one to five target ICD-9 codes (i.e. dyspnea, pulmonary fibrosis, cholestatic jaundice, chronic hepatitis, or hepatotoxicity) associated with a nitrofurantoin-induced adverse event. After manual chart inspection of these 641 suspected cases, 89% were deemed to have no drug-related adverse event, 5.1% had a minor side effect, 1.9% were allergic reactions, and 3.9% (25/641) were identified as possible pulmonary or hepatic nitrofurantoin-induced adverse

events (Figure 3). Five (0.8%) of the 25 possible serious adverse event cases were rated as high suspicion for nitrofurantoin toxicity and 20 cases as possible suspicion for an adverse drug effect (3.1%) (Table 2). Of the high suspicion cases, four patients were identified with pulmonary toxicity and one patient with hepatotoxicity; four of the five high suspicion cases used nitrofurantoin for chronic use. Four individuals with existing interstitial lung disease had worsened dyspnea while on nitrofurantoin, accounting for four of the seven (57%) Possible A individuals.

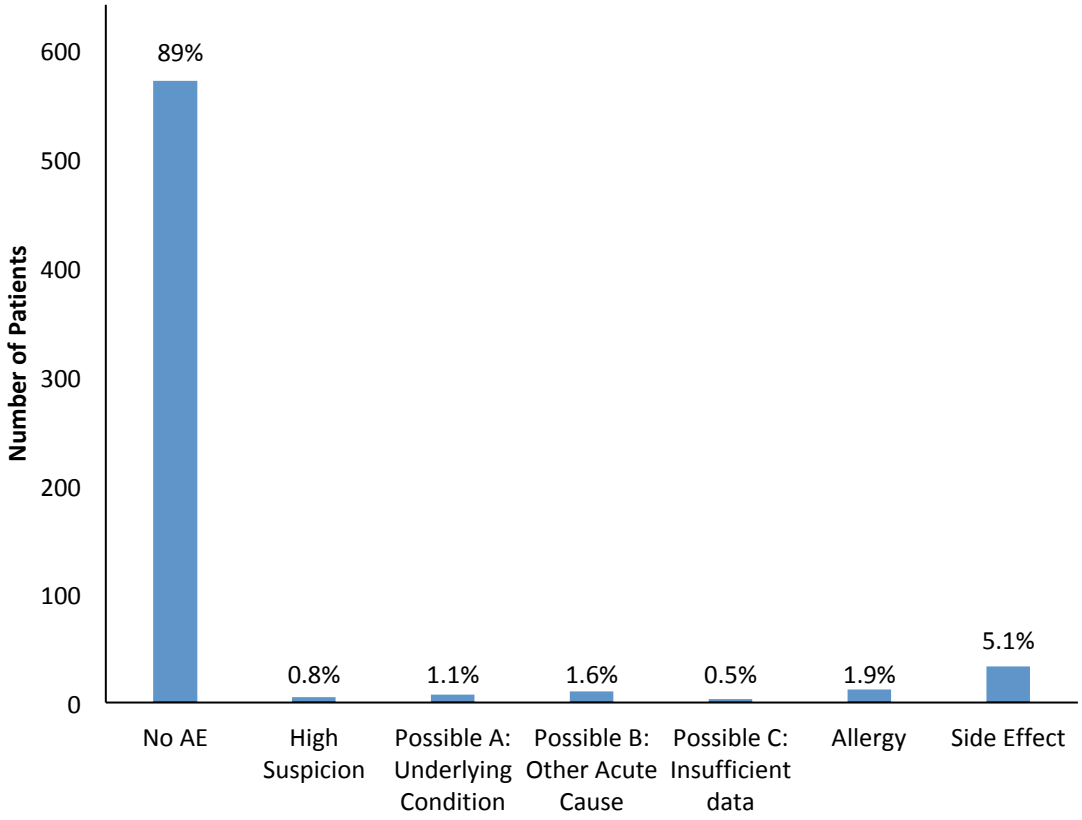

Figure 3. Nitrofurantoin-associated adverse event incidence

Table 2. Summary of Nitrofurantoin-induced Adverse Event (AE) Cases

AE[a]	Case No.	Age at time of AE	Sex	Dose mg/d	Length of Use[b]	eGFR closest to NF AE, mL/min per 1.73 m^2
High Suspicion	1	73	F	100	6 y	23
High Suspicion	2	82	F	200	6 days, short courses	>60
High Suspicion	3	82	F	50	1 y	38
High Suspicion	4	69	F	50	30 y	60
High Suspicion	5	72	F	100	2 y	>60
Possible A	6	77	F	200	3 short courses	>60
Possible A	7	73	F	200	2 short courses	48
Possible A	8	74	F	200	3 short courses	78
Possible A	9	86	F	200	1 short courses	16
Possible A	10	75	F	200	7 s, 3 l mo	40
Possible A	11	94	M	200	2 short courses	>60
Possible A	12	69	F	Not listed	y	>60
Possible B	13	86	F	50	3 y	48
Possible B	14	87	F	50	1 y	58
Possible B	15	85	F	200	1 short courses	>60
Possible B	16	77	F	100	5 mo	>60
Possible B	17	68	F	200	2 short courses	>60
Possible B	18	76	F	400	12 short courses	52
Possible B	19	83	F	100	5 s, 6 l mo	>60
Possible B	20	82	F	50	? y	46
Possible B	21	69	F	100	mo	-
Possible B	22	75	F	50	? y	25
Possible C	23	73	F	200	2 short courses	>60
Possible C	24	68	F	200	short courses	>60
Possible C	25	85	F	200	short courses	>60

[a]See Table 1 for definitions of AE categories. [b]Short course defined as less than 30 tablets.

AEs were further classified according to age, sex, drug exposure, and eGFR. There were no differences between the three age groups (P = .34) (Figure 4), but a difference in sex between the 25 individuals with possible AEs was noted; women were more likely to have a possible AE (P = .04), although there was only one man in this category (Figure 5). Estimated GFR was available only for the 25 individuals who were suspected of having nitrofurantoin-induced AEs, but the distribution above and below 60 mL/min per 1.73 m^2 appeared similar (Figure 6).

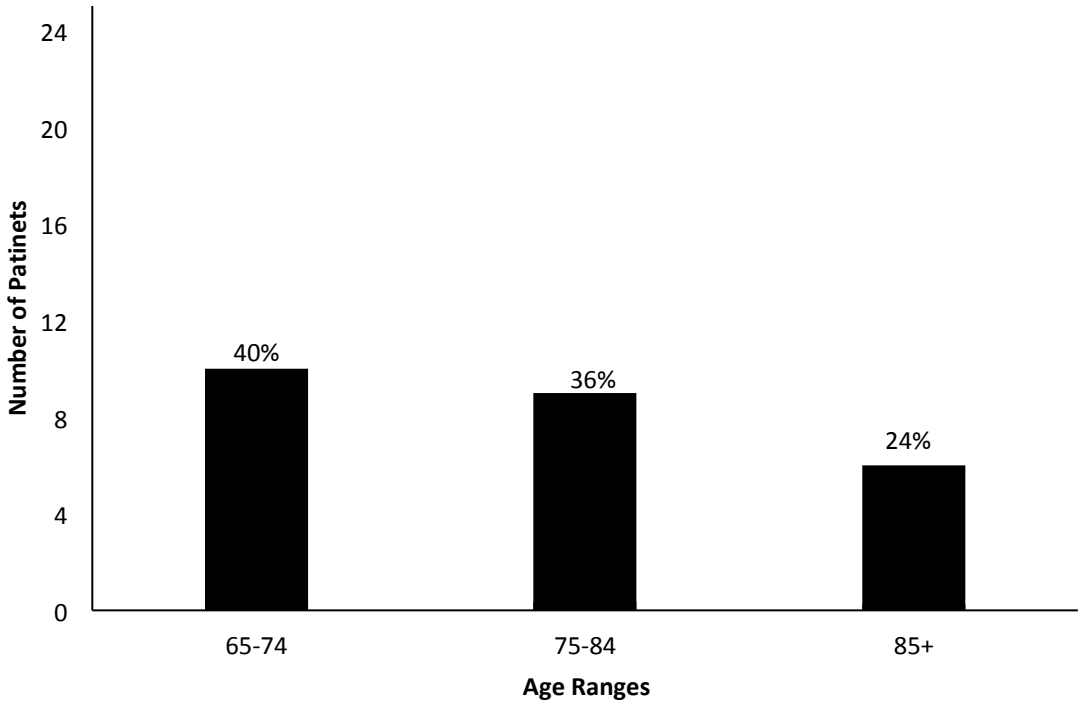

Figure 4. NF-associated AE distributed by age

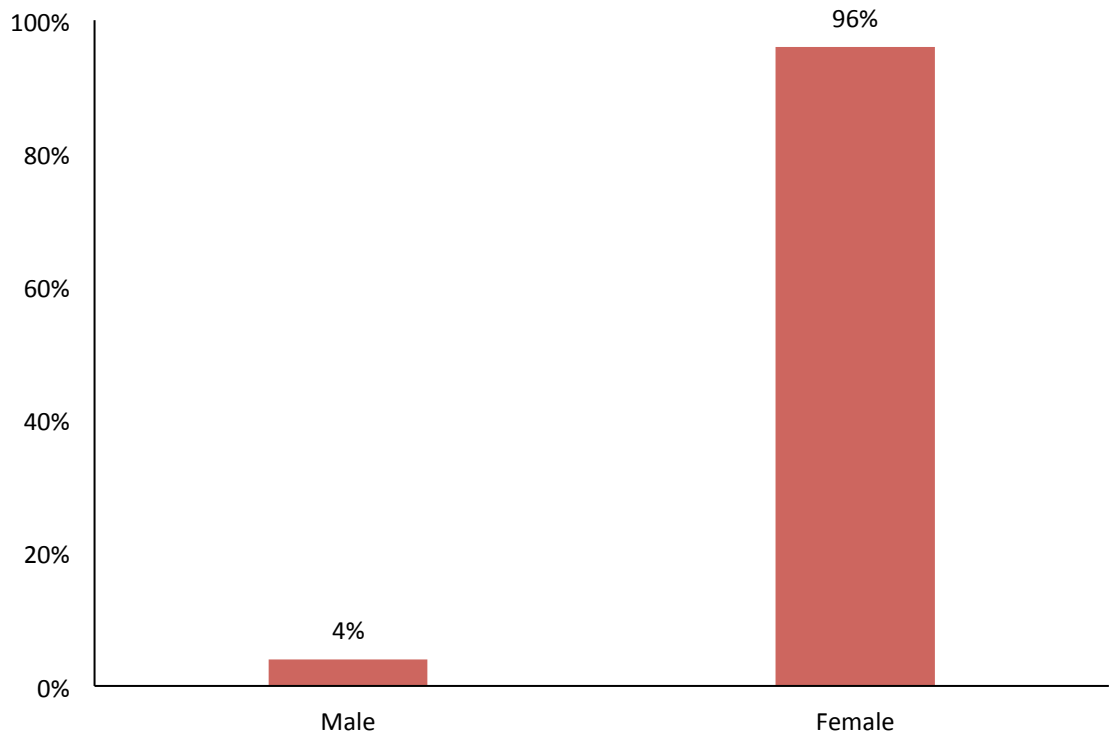

Figure 5. NF-associated AE distributed by sex

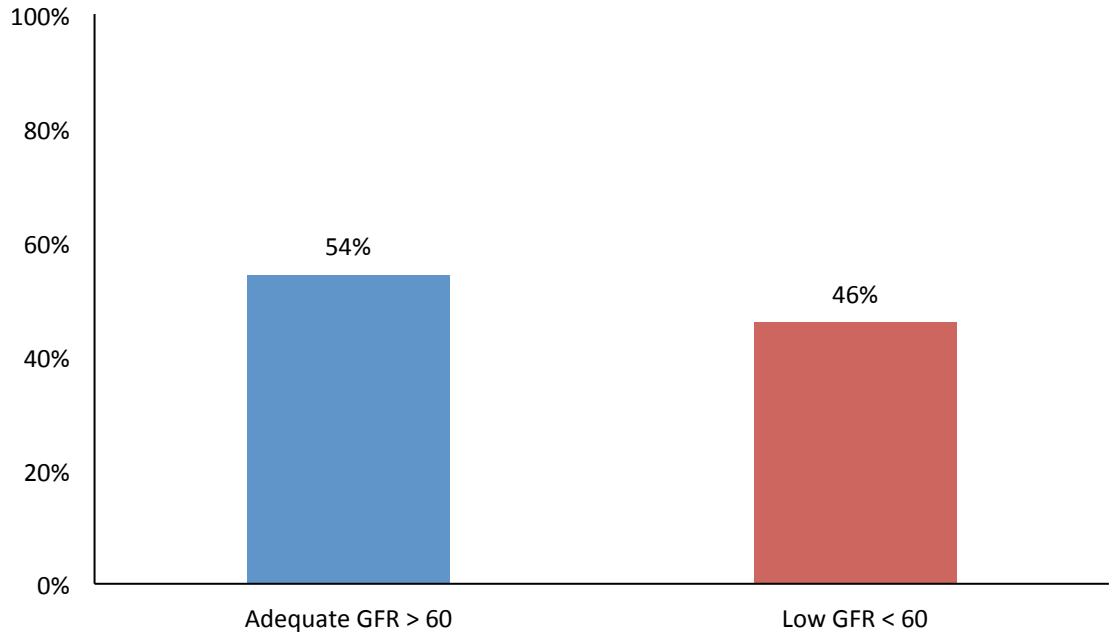

Figure 6. NF-associated AE and estimated glomerular filtration rate

When evaluating chronicity of use, it was found that 80% (4/5) of high suspicion individuals took nitrofurantoin for at least 1 month, whereas 14% of Possible A, 40% of possible B, and none of Possible C individuals received long-term nitrofurantoin (Figure 7). Among the patients who took nitrofurantoin chronically, 45% (4/9) patients were age 65-74, 33% were age 75-84, and 22% were age 85 and older (Figure 8).

Out of the patients with a possible AE, side effect, or allergy, it was noted whether or not nitrofurantoin was listed as an allergy in their chart. Overall, 41% of these patients had nitrofurantoin listed as an allergy, the highest reporting in the allergy group (83%) and lowest in the adverse event group (32%) (Figure 9).

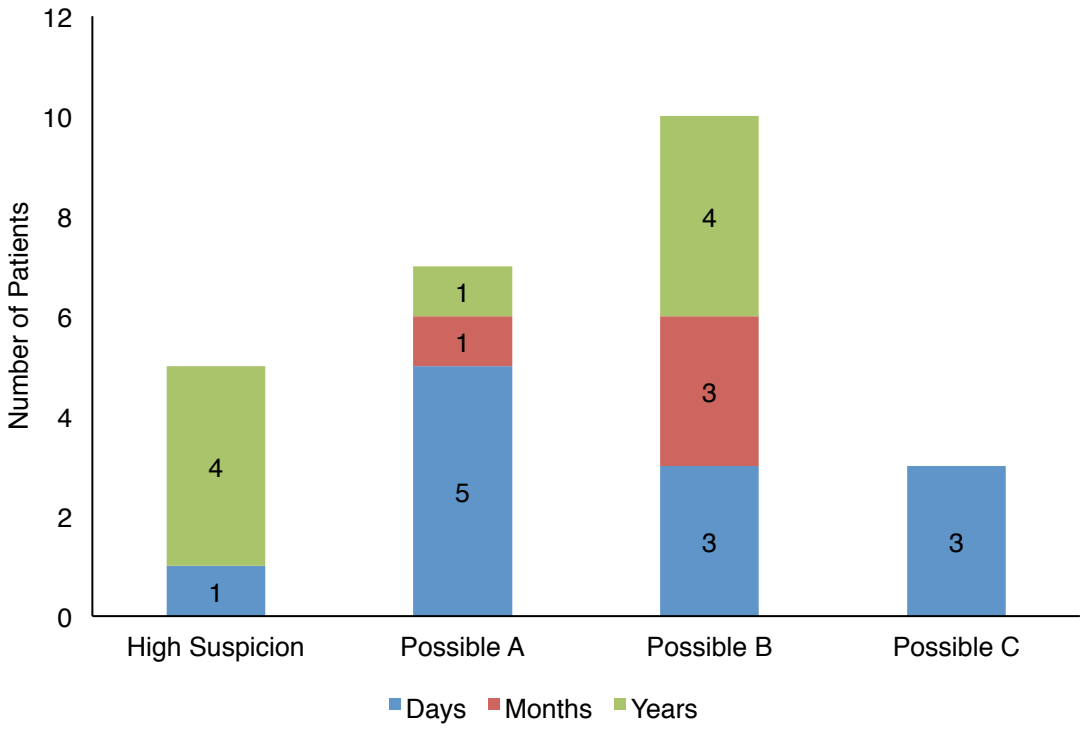

Figure 7. NF-associated AE type and length of use

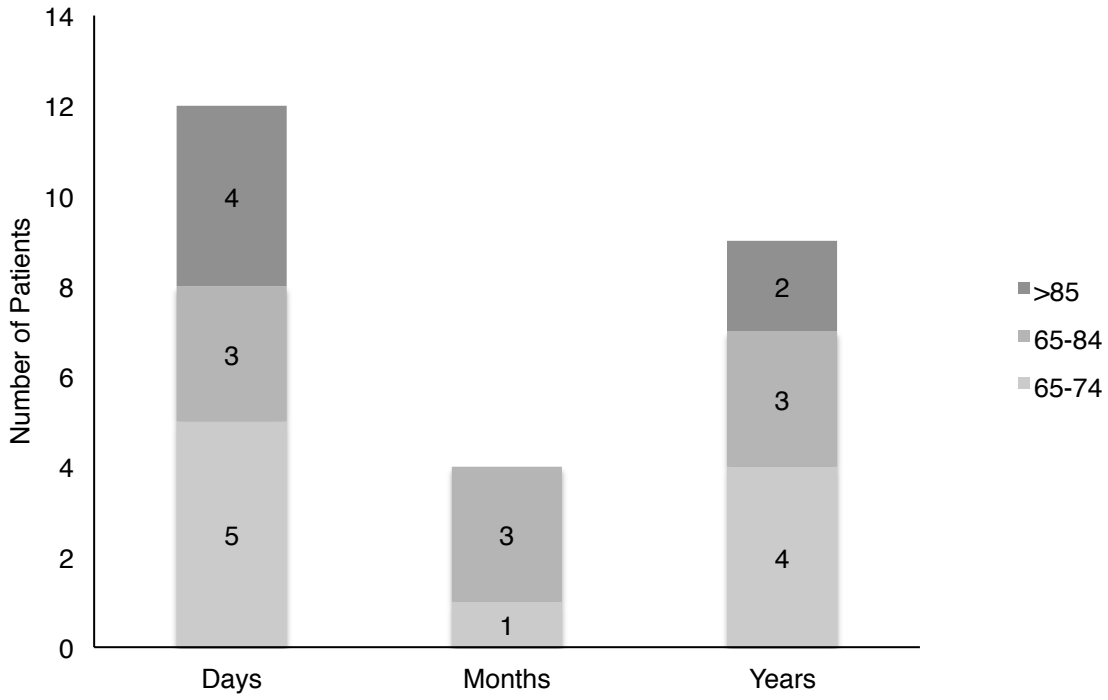

Figure 8. NF-associated AE correlated with duration of use and age

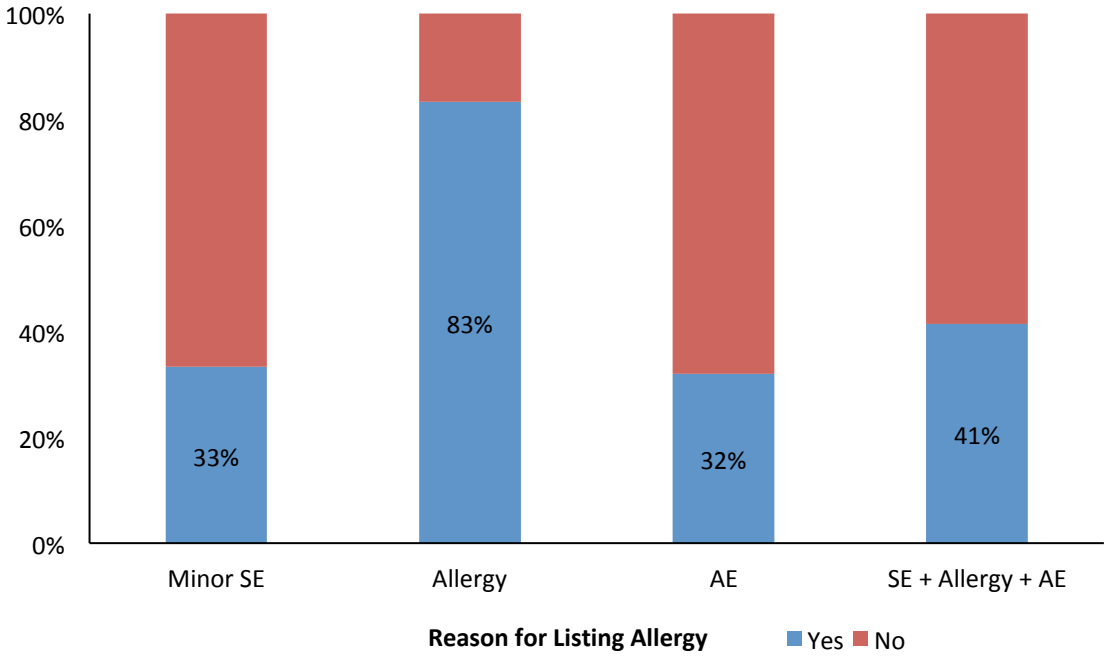

Figure 9. Electronic Medical Record Recording for Nitrofurantoin Allergies

When the Naranjo Adverse Drug Reaction Probability Scale was used, all high suspicion individuals had a scored of 4 and were considered to have a possible reaction. One Possible B individual had a score of 4, the other 19 possible cases had a score of 1 to 3, and none had a score of 0 or less.

Discussion

Despite the placement of nitrofurantoin on the Beers list, it is commonly prescribed in individuals aged 65 and older in a large multispecialty academic health system. Of the 3,400 individuals prescribed nitrofurantoin, 25 were identified over a five-year period with pulmonary or hepatic diagnoses possibly associated with nitrofurantoin, five cases of which were felt to be highly likely to be a serious nitrofurantoin-induced adverse event. Overall, 0.7% (25/3,400) of individuals had possible serious pulmonary or hepatic adverse events to nitrofurantoin, and 0.15% (5/3,400) were classified as highly likely to have had a serious pulmonary or hepatic reaction. The majority of high suspicion cases used nitrofurantoin chronically; the most common reasons for chronic use as discerned according to chart inspection were for neurogenic bladder and idiopathic recurrent UTIs.

In a previous study, pulmonary toxicity due to nitrofurantoin occurred in 0.001% of individuals and hepatic toxicity due to nitrofurantoin use occurred in 0.0003% of individuals.[11] A recent systematic review[12] found no pulmonary or hepatotoxic events related to nitrofurantoin use in 4,807 individuals from 27 controlled trials, although the trials were of short-term use and predominantly in

younger individuals. Overall, nitrofurantoin-induced toxicity was 5% to 16% in the 17 of 27 studies, reporting toxicity and was mostly mild, reversible gastrointestinal side effects. A recently published study[13] did not find an overall greater risk of lung injury in individuals given nitrofurantoin than in those given other antimicrobials for cystitis, although the group taking nitrofurantoin for at least 14 days had a higher risk of lung injury than those taking it for a shorter duration.[13]

Although an adverse reaction to a medication is not physiologic allergy, recording an adverse event to a medication as an allergy in the patient's electronic medical record is the only means our electronic system warns future providers from prescribing the potentially inappropriate medication again. Given several patients with a possible adverse event, minor side effect, and allergy, a total of only 41% had nitrofurantoin listed as an allergy in the electronic medical record. Of that, 17% of patients with a true allergy and 68% of patients with a nitrofurantoin-associated adverse event did not have nitrofurantoin listed in their chart as an allergy. This is an area for improvement in order to decrease future adverse events in a population that is at high risk for developing another nitrofurantoin-induced adverse event.

The current study results may be skewed because of possible pre-exclusion of nitrofurantoin prescriptions to individuals with a low eGFR. Although, nitrofurantoin use was common despite recommendations during the time of the study to avoid use in older adults and in particular in those with creatinine

clearance less than 60 mL/min per 1.73 m^2. The 25 individuals with possible nitrofurantoin-associated adverse events were almost equally divided between those with an eGFR above and below 60 mL/min per 1.73 m^2. Treatment failure, which has been a concern with use of nitrofurantoin in older populations, was not evaluated. Findings from a recent study in woman aged 65 and older treated with nitrofurantoin for UTIs found no difference in treatment response with a mild or moderate reduction in eGFR.[14]

Although peripheral neuropathy is another serious adverse event associated with nitrofurantoin use, it was decided not to include ICD9 codes for peripheral neuropathy because of the potential difficulty assigning nitrofurantoin as causation for this common problem in older adults. There may have been several other confounders such as diabetes mellitus, alcohol consumption, and idiopathic neuropathy, which create difficulty to assign nitrofurantoin as the causal agent. Nonetheless, by omitting this potential side effect, a common serious reaction to nitrofurantoin use may have been underreported. However, there was no evidence of nitrofurantoin-induced neuropathy found in the 641 charts reviewed for possible pulmonary or hepatic complications of the medication.

There are several limitations to this study. This retrospective review of EHRs depended on documentation of complaints and coding, medication adherence, and follow-up. Lack of proper documentation could have led to inaccurate reporting of adverse events. If individuals developed side effects and

did not return to the health system, their events would not have been captured. In addition, medication adherence was not confirmed using pill count or other measures but relied solely on prescribing information. Furthermore, the retrospective analysis did not allow for interviews or prospectively evaluate data, which would be particularly helpful to assess adverse drug events; likewise, the retrospective analysis did not provide the medical reasoning for nitrofurantoin selection. An effort was made to minimize subjectivity by using multiple chart reviewers and a decision matrix; interpretation of adverse events could be a source of incidence under or over reporting. Lastly, limited demographic information may make application of the findings to individual practitioners difficult.

The 0.8% to 4% incidence of AEs reported here is of concern but should not prohibit nitrofurantoin prescriptions in older adults. Overall, the findings support the recently updated Beers Criteria guidelines,[2] which advocate avoiding chronic use in older adults and in individuals with creatinine clearance less than 30 mL/min per 1.73 m^2, but because individuals younger than 65 were not included in the study, it could not be determined whether there were age-related differences in hepatic and pulmonary complications to nitrofurantoin. The initial inclusion of nitrofurantoin on the Beers List was at least partially based on lack of efficacy with age-related decline in renal function, so it is possible that its inclusion may no longer be justified.

There are several potential quality improvement initiatives UT

Southwestern should consider given this information in order to improve patient safety with nitrofurantoin use. Given the inadequate allergy-reporting rate, the institution would benefit from tighter control of allergy and drug adverse event documentation. A quality improvement project could be initiated to best address medication adverse events in a similar way to how allergies are reported. Secondly, there was a correlation to patients with underlying lung disease and a higher rate of nitrofurantoin-induced adverse events. Therefore, UT Southwestern could consider a quality improvement intervention to monitor for adverse events with high-risk patients in a standardized manner or prevent high-risk patients from receiving the medication in the first place. Lastly, another population at high risk for a nitrofurantoin-induced adverse event is those patients taking nitrofurantoin chronically for UTI prophylaxis. UT Southwestern could target minimizing the risks associated with long-term use of nitrofurantoin, monitoring them for side effects, or decreasing the amount of prophylactic nitrofurantoin prescriptions. These are a few of many ways UT Southwestern could utilize quality improvement interventions to decrease the number of nitrofurantoin adverse events in the geriatric population.

In summary, these findings suggest that individuals with chronic lung disease (e.g. interstitial lung disease, pulmonary fibrosis) should avoid nitrofurantoin and that particular care should be taken when prescribing nitrofurantoin for long-term use. However, there is little evidence found to prohibit short-term use of nitrofurantoin in patients without underlying chronic lung

disease. Although caution should be exercised with all medications, it is hoped that this analysis will help close the quality gap regarding nitrofurantoin use in the geriatric population, stimulate greater reporting and risk assessment of nitrofurantoin use, provide more tangible data to inform providers, and clarify the risk factors for adverse events associated with nitrofurantoin in older adults.

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VITAE

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