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Emergency Department Visits and Hospitalizations for Digoxin Toxicity—United States, 2005–2010

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Abstract

Background—Recent data on digoxin prescribing and adverse events are lacking but could help inform the management of digoxin in contemporary heart failure treatment.

Methods and Results—We determined nationally-representative numbers and rates of emergency department (ED) visits for digoxin toxicity in the United States using 2005–2010 reports from the National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance project and the National Ambulatory (and Hospital Ambulatory) Medical Care Surveys. Based on 441 cases, an estimated 5,156 (95% confidence interval [CI], 2,663–7,648) ED visits for digoxin toxicity occurred annually in the United States; over three-fourths (78.8% [95% CI, 73.5%–84.1%]) resulted in hospitalization. Serum digoxin level was ≥2.0 ng/mL for 95.8% (95% CI, 93.2%–98.4%) of estimated ED visits with levels reported (n=251 cases). The rate of ED visits per 10,000 outpatient prescription visits among patients ≥85 years was twice that of patients 40–84 years (rate ratio, 2.4 [95% CI, 1.2–5.0]); among females, the rate was twice that of males (rate ratio, 2.3 [95% CI, 1.1–4.7]). Digoxin toxicity accounted for an estimated 1.0% (95% CI, 0.6%–1.4%) of ED visits for all adverse drug events (ADEs) among patients ≥40 years, but an estimated 3.3% (95% CI, 2.3%–4.4%) of ED visits and 5.9% (95% CI, 4.0%–7.9%) of hospitalizations for all ADEs among patients ≥85 years. Estimated annual ED visits and hospitalizations remained relatively constant from 2005–2010.

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Disclosures

None.

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Conclusion—Digoxin toxicity is not declining; more careful prescribing to high-risk groups and improved monitoring of serum levels might be needed to reduce morbidity from outpatient digoxin use.

Keywords

adverse drug event; rehospitalization; heart failure; emergency department; digoxin

Introduction

Congestive heart failure causes over 900,000 admissions annually in the United States with a readmission rate exceeding 20% [1]. Many hospitals have implemented quality improvement initiatives to lower the burden of heart failure-related readmissions, and financial incentives from the Centers for Medicare and Medicaid Services for reducing such readmissions have recently been established [2, 3]. Despite interest in preventing heart failure admissions, novel therapies to reduce the frequency of heart failure complications have not been approved for use in United States in recent years. Neither large-scale clinical trials of novel pharmacological agents nor medical devices that detect increases in cardiac filling pressures have proven effective in decreasing heart failure hospitalizations [4, 5]. Digoxin, one of the oldest available treatments for heart failure, has declined in use over the past two decades in favor of agents with demonstrated mortality benefit but remains a common adjunctive therapy for heart failure, particularly in patients with refractory symptoms [6]. To further curb heart failure-related hospitalizations, some have recently suggested re-evaluating digoxin's role in contemporary heart failure treatment [4, 7].

One of the important limitations to digoxin use remains its narrow therapeutic index as it contributes to development of cardiac and non-cardiac (e.g., central nervous system, gastrointestinal) toxicities [8]. Understanding the current epidemiology of digoxin toxicity could provide additional context for renewed considerations of digoxin use in heart failure. We used nationally representative public health surveillance data from the United States to estimate the frequency and rates of emergency department (ED) visits and hospitalizations for digoxin toxicity and to characterize the nature of these visits.

Methods

National estimates of the number of ED visits and subsequent hospitalizations for adverse drug events (ADEs) were based on data from the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) project, a national stratified probability sample comprised of 63 hospitals in the United States and its territories; this surveillance system, including its performance characteristics, has been previously described in detail [9–11]. For this analysis, only data from the 58 participating non-pediatric hospitals were used. In brief, trained abstractors at each hospital review clinical records of every ED visit to identify conditions that the treating clinician explicitly attributed to the use of a drug (i.e., prescription and over-the-counter medications, vaccines, and herbals/dietary supplements) or drug-specific adverse effects. Abstractors record up to 2 medications implicated in each ADE by the treating clinician in addition to narrative

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descriptions of the incidents, including physician diagnosis and clinical testing. Narrative descriptions are then coded using the Medical Dictionary for Regulatory Activities (MedDRA), an international terminology used to analyze ADE reports [12]. In this analysis, hospitalization was defined as admission to an inpatient unit of the healthcare facility, transfer to another healthcare facility, or billed as a hospital observation stay.

Patients younger than 40 years were involved in only 6.4% of all cases of digoxin-related adverse events reported to NEISS-CADES and were excluded from analysis. Cases of digoxin-related adverse events reported to NEISS-CADES from ED visits made between January 1, 2005 and December 31, 2010 were included if evidence of digoxin toxicity was present as indicated by documentation in the medical record narrative of any one of the following terms: “digoxin toxicity” or “drug toxicity,” documentation of administration of a digoxin dose greater than prescribed or intended (i.e., medication error), an elevated digoxin level (≥2.0 ng/mL), or at least one of the following signs/symptoms consistent with digoxin toxicity: cardiac dysrhythmias, gastrointestinal disturbances (anorexia, nausea, vomiting, or diarrhea), mental disturbances (anxiety, depression, delirium, hallucinations, weakness, apathy, confusion, or decreased level of consciousness), visual disturbances, or leg cramps. Clinical symptoms associated with digoxin toxicity were characterized based on MedDRA terms and grouped into hierarchical and mutually exclusive categories. To ensure that reported symptoms were related to digoxin and not another medication implicated in the ED visit, clinical symptoms were analyzed only for cases in which digoxin was the only offending medication (i.e., a second implicated medication was not recorded) and at least one clinical symptom was provided.

National estimates of the number of ambulatory care visits at which digoxin was prescribed were based on 2 national cross-sectional surveys of ambulatory medical care services: the National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS), which involve a multistage sampling design of ambulatory care visits to non-federally employed office-based physicians and to EDs and outpatient departments of noninstitutional general and short-stay hospitals, exclusive of federal, military, and Veterans Administration hospitals [13]. For this analysis, we refer to all NAMCS/NHAMCS ambulatory care visits at which digoxin was prescribed or continued as “outpatient prescription visits.” We used public use data files for 2005–2010 to identify ambulatory care visits at which digoxin was prescribed or continued. Visits by patients younger than 40 years comprised 5.9% of all outpatient prescription visits for digoxin reported to NAMCS/NHAMCS and were excluded from analysis. Digoxin was identified by searching the 8 medication fields in each NAMCS/NHAMCS dataset for the Multum Lexicon Drug Database codes identifying relevant generic ingredients (i.e., digoxin, digitoxin, digitalis) [14–16].

Each selected NEISS-CADES, NAMCS, and NHAMCS record was accompanied by a sample weight based on inverse probability of selection, adjusted for nonresponse and post-stratified to adjust for the number of annual hospital ED visits (NEISS-CADES), and adjusted for nonresponse and population changes incorporating weight smoothing (NAMCS/NHAMCS) [9, 13, 17]. National estimates and percentages of ED visits and outpatient prescription visits, as well as corresponding 95% confidence intervals (CIs) were calculated

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using the SURVEYMEANS procedure in SAS (version 9.3; SAS Institute Inc, Cary, North Carolina) to account for the sample weights and complex sample designs. The resulting frequency estimates and confidence limits derived from NEISS-CADES and NAMCS/NHAMCS data were divided by 2 for the time periods 2005–2006, 2007–2008, and 2009–2010 to obtain annual estimates representing these three periods; and were divided by 6 for the time period 2005–2010 to obtain annual estimates representing the entire study period. Estimates based on small numbers of cases (<20 cases for NEISS-CADES and <30 cases for NAMCS/NHAMCS) or with a coefficient of variation greater than 30% were considered statistically unstable and are not presented here.

To estimate rates of ED visits for digoxin toxicity relative to outpatient medication use, we divided the estimated number of ED visits for digoxin toxicity by the estimated number of outpatient prescription visits for digoxin. Calculation of the 95% CI for each rate incorporated variance estimates for both numerator and denominator components of the corresponding rate estimate [18]. Because these components were calculated from separate surveillance systems, they were treated as independent (and, thus, as having zero covariance).

Rate ratios (RRs) were used to compare rates of ED visits for digoxin toxicity relative to outpatient medication use between different patient populations. Estimated 95% CIs for the RRs were calculated using an initial logarithmic transformation and incorporated the estimated variances of the numerators and denominators of both component rate estimates [18, 19]. The component rate estimates were again assumed to be independent across patient populations.

Data collection, management, quality assurance, and analyses were determined to be public health surveillance activities by the Centers for Disease Control and Prevention (CDC) and U.S. Food and Drug Administration human subjects oversight bodies and, therefore, did not require human subjects review or institutional review board approval.

Results

Between 2005 and 2010, 443 cases of digoxin-related adverse events among patients 40 years or older were reported to NEISS-CADES. Two cases were digoxin-related allergic reactions. The remaining 441 met criteria for inclusion in the analysis. Based on these 441 cases, an estimated 5,156 ED visits (95% CI, 2,663–7,648) for digoxin toxicity among patients 40 years or older occurred annually in the United States during 2005–2010 (Table 1). The estimated number of ED visits for digoxin toxicity remained relatively constant over time. The majority of ED visits for digoxin toxicity occurred among females (67.8% [95% CI, 62.9%–72.6%]), patients 70 years or older (79.1% [95% CI, 73.5%–84.7%]), and patients of white race (70.3% [95% CI, 56.7%–83.8%]). During 2005–2010, digoxin toxicity accounted for an estimated 1.0% (95% CI, 0.6%–1.4%) of ED visits for all ADEs among patients 40 years or older: an estimated 0.7% (95% CI, 0.4%–1.1%) of ED visits for all ADEs among patients 40–84 years, and an estimated 3.3% (95% CI, 2.3%–4.4%) of ED visits for all ADEs among patients 85 years or older.

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Overall, over three-fourths (78.8% [95% CI, 73.5%–84.1%]) of estimated ED visits for digoxin toxicity resulted in hospitalization; this was also true across all age groups (Table 1). In contrast, for medications other than digoxin, the estimated proportion of ED visits for ADEs resulting in hospitalization was 20.6% (95% CI, 16.8%–24.3%) in patients 40–69 years, 36.5% (95% CI, 30.6%–42.4%) in patients 70–84 years, and 43.2% (95% CI, 36.8%–49.7%) in patients 85 years or older. Among patients 85 years or older, digoxin toxicity was the cause of an estimated 5.9% (95% CI, 4.0%–7.9%) of hospitalizations related to all ADEs. The proportion of ED visits for digoxin toxicity resulting in hospitalization remained relatively constant over time (Table 1).

Among cases where the serum digoxin level was recorded (251 cases), a level ≥2.0 ng/mL was present in an estimated 95.8% (95% CI, 93.2%–98.4%) of ED visits for digoxin toxicity (Table 2). In 369 of the 441 reported cases, digoxin was considered the only offending drug related to the ED visit. Clinical symptoms were recorded for 365 of these cases (Table 3). In over two-thirds of estimated ED visits, symptoms affecting the central nervous system (25.2% [95% CI, 17.4%–33.1%]) or cardiovascular system (44.5% [95% CI, 37.3%–51.7%]) were recorded. Cases in which only gastrointestinal symptoms were recorded comprised a minority of ED visits for digoxin toxicity (9.7% [95% CI, 5.8%–15.5%]). All other types of symptoms (e.g., fatigue, myalgias) were documented in an estimated 11.9% (95% CI, 8.0%–15.8%) of ED visits. Medication errors (i.e., administration of a digoxin dose higher than prescribed or intended) were documented in too few cases (11 of 369 [3.0%] cases where digoxin was the only offending drug documented) to be able to report a national estimate.

Accounting for the number of outpatient prescription visits for digoxin, estimated rates of ED visits for digoxin toxicity were essentially constant throughout the study period (Table 4). However, the rates of ED visits for digoxin toxicity increased with age: the rate of ED visits per 10,000 outpatient prescription visits among patients 85 years or older was twice that of patients younger than 85 years (10.8 [95% CI, 6.1–15.6] vs. 4.5 [95% CI, 1.9–7.0] ED visits per 10,000 outpatient prescription visits; RR, 2.4 [95% CI, 1.2–5.0]); in particular the rate was 3 times that of patients 40–69 years (RR, 3.0 [95% CI, 1.4–6.2]). Females had twice the rate of ED visits for digoxin toxicity when compared with males (7.8 [95% CI, 4.2–11.5] vs. 3.5 [95% CI, 1.5–5.4] ED visits per 10,000 outpatient prescription visits; RR, 2.3 [95% CI, 1.1–4.7]).

Discussion

In 1997, over 20 million prescriptions for digoxin were written in the United States, placing it among the 20 most commonly prescribed medications [20]. In ensuing years, after the Digoxin Investigation Group (DIG) trial found that digoxin use reduced the rate of hospitalizations in heart failure patients but had no effect on mortality, digoxin lost favor as a first-line agent in the treatment of heart failure since other medications with a demonstrated mortality benefit had emerged [21–23]. The annual number of prescriptions for digoxin and admissions for digoxin toxicity subsequently declined through 2004 [24, 25]. Our analysis indicates that ED visits for digoxin toxicity did not decrease further during 2005–2010, with over 5,000 estimated ED visits occurring annually.

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These events involved considerable morbidity. Over three-quarters of estimated ED visits for digoxin toxicity resulted in hospitalizations. In addition, we estimated that over one-fourth of ED visits for digoxin toxicity involved symptoms affecting the central nervous system and that arrhythmias and syncopal episodes comprised many of the cardiovascular manifestations, the principal presentation for almost half of ED visits. Our analysis might actually underestimate the proportion of ED visits involving these severe presenting symptoms, since in 47 cases only the treating clinician's diagnosis of "digoxin toxicity" was recorded (without the patient's exact presenting symptoms).

Accounting for outpatient prescription frequency, we found females and older adults to have disproportionately high rates of ED visits for digoxin toxicity. It remains debated whether females are biologically more susceptible to development of digoxin toxicity [26, 27]; however, our data suggest that, in practice, females are affected by digoxin toxicity at higher rates. Digoxin toxicity was also an important reason for ED visits for ADEs among older adults, accounting for over 1 of 20 of such visits in adults 85 years or older. In contrast to other medications commonly implicated in emergent hospitalizations for ADEs in older adults, which lead to hospitalization in an estimated 20%–50% of visits [28], we found the estimated rate of hospitalization for digoxin toxicity to be 75%. Older adults are at greater risk for adverse effects from all medications because of altered pharmacokinetics or polypharmacy [29]. Older adults with heart failure might furthermore be at particular risk for developing digoxin toxicity due to concomitant comorbidities such as hypokalemia (from diuretic use) or renal impairment [29, 30].

Potential benefits of prescribing digoxin for heart failure patients have been reported based on secondary analyses of DIG trial data [31–34]. New clinical trials would be needed to confirm the efficacy of digoxin as an adjunct to contemporary medical therapy for heart failure. This study does not examine the risk/benefit ratio of increased use of digoxin, but we have used public health surveillance data to focus on the risk of digoxin toxicity and provide insight into potential ways to minimize the harms resulting from digoxin use. By identifying patient subpopulations at increased risk of digoxin toxicity, our findings point to the following considerations if digoxin is to be increasingly used as an adjunctive measure to prevent heart failure admissions.

First, careful patient selection for digoxin therapy, proper initial dosing, and heightened surveillance for high-risk patients, such as females and older adults, might mitigate the burden of ED visits and hospitalizations for digoxin toxicity. Second, consistent guidance for what constitutes a therapeutic serum digoxin level might also reduce the incidence of patients presenting with toxicity. The levels reported for most ED visits for digoxin toxicity were ≥2.0 ng/mL. Clinical practice guidelines suggest that serum digoxin levels 0.5–0.9 ng/mL are therapeutic for heart failure and that higher levels might be harmful [35]. However, dissemination of 0.5–0.9 ng/mL as the standard reference range is inconsistent; many sources still indicate 2.0 ng/mL as the upper level of the therapeutic range for serum digoxin levels [8]. Furthermore, many hospital laboratories still consider digoxin levels of 2.0 ng/mL to be within normal range [36]. Targeting the lower range would likely further reduce the number of patients who inadvertently experience digoxin toxicity from serum digoxin levels that are clearly supratherapeutic. Third, incorporating prevention of digoxin

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toxicity into current strategies for reducing heart failure readmissions represents a potential means of intervention for the at-risk population. This is corroborated by data indicating increased risk of hospitalization for digoxin toxicity following hospitalization [37]. Existing programs for reducing heart failure readmissions focus on medication reconciliation, patient compliance with medications, electronic medical orders, and careful and close follow-up during transitions of care from the inpatient to outpatient setting [38]. To prevent digoxin toxicity, merely ensuring that patients are taking the medication as prescribed is likely to have limited utility, particularly considering that few of our reported cases were due to medication errors. However, given their potential ability to manage patients whose care is coordinated by multiple providers, readmission reduction programs may provide a framework that can be leveraged to improve monitoring and follow-up of digoxin levels.

This study's findings should be interpreted in the context of the limitations of public health surveillance data. First, NEISS-CADES only captures ADEs resulting in ED visits or emergent hospitalizations. Thus, clinical episodes of digoxin toxicity resulting in lower levels of care (e.g., physician office visits) or direct admissions to the hospital would not have been identified. Additionally, digoxin toxicity might go unrecognized during an ED visit and would not be reported if it were diagnosed during hospitalization after the ED visit. NEISS-CADES also does not include data on length of stay for patients hospitalized for digoxin toxicity. Second, NAMCS/NHAMCS imperfectly measure outpatient prescribing frequency as they exclude prescriptions initiated by phone and e-mail contacts as well as prescriptions initiated in nursing homes, in ambulatory surgery centers, or provided at hospital discharge. However, we would not expect this to affect the relative magnitude of the risks of digoxin toxicity between genders. Although NAMCS/NHAMCS data may be underestimates of outpatient prescription visits for older adults, previous studies have also found older adults to be at higher risk of digoxin toxicity compared to younger patients [39, 40]. Third, we did not have sufficient information from all cases to ascertain the indication for digoxin use; thus these data might include patients being treated for indications other than heart failure (e.g., atrial fibrillation). Fourth, we did not have information in all cases about such variables as electrolyte levels, renal function, and concomitant medications and thus could not fully characterize factors leading to digoxin toxicity. This is important in that digoxin might be currently considered more often for patients with advanced heart failure, who have the greatest risk for renal impairment and thus digoxin toxicity. Fifth, we do not have a record of the indication for hospitalization in our cases. As patients with heart failure have high rates of hospitalization in general, some of the hospitalizations described could have been for patients' underlying illnesses rather than digoxin use per se. However, given that the incident emergency department visits were related to use of digoxin, it is likely that most of the subsequent hospitalizations were related to digoxin use as well.

Digoxin continues to have a niche in the treatment of patients with symptomatic heart failure who are refractory to other treatments [41]. National public health surveillance data indicate that digoxin use and the burden of digoxin toxicity as measured by ED visits and hospitalizations did not decline from 2005 through 2010. The lack of decline in digoxin toxicity over this time period could be due to a number reasons, including unchanged frequency of digoxin prescribing during this time, continued used of high reference ranges (e.g., an upper limit of 2.0 ng/mL) for serum digoxin levels, or lack of effective strategies

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targeted at safely managing digoxin therapy among patients at highest risk of adverse events. Efforts to minimize morbidity from toxicity when digoxin use is considered might require prevention strategies focused on identifying the patient populations most likely to benefit from digoxin therapy, careful prescribing to high-risk populations (i.e., females and older adults) and improving monitoring and management of digoxin levels, including promoting adherence to lower ranges (e.g., 0.5–0.9 ng/mL) for serum digoxin levels.

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References

1. HCUPnet. Healthcare Cost and Utilization Product (HCUP). Agency for Healthcare Research and Quality; 2010. Available at: http://hcupnet.ahrq.gov [Accessed August 27, 2013]
2. Centers for Medicare and Medicaid Services. [Accessed August 27, 2013] Medicare program; hospital inpatient prospective payment systems for acute care hospitals and the long-term care hospital prospective payment system and fiscal year 2013 rates; hospitals' resident caps for graduate medical education payment purposes; quality reporting requirements for specific providers and for ambulatory surgical centers. Available at: https://www.federalregister.gov/articles/2012/08/31/2012-19079/medicare-program-hospital-inpatient-prospective-payment-systems-for-acute-care-hospitals-and-the
3. Fiegl, C. 2,200 hospitals face Medicare pay penalty for readmissions. American Medical News; Available at: http://www.ama-assn.org/amednews/2012/08/27/gvsb0827.htm [Accessed August 27, 2013]
4. Gheorghiade M, Harinstein ME, Filippatos GS. Digoxin for the treatment of chronic and acute heart failure syndromes. Acute Card Care. 2009; 11:83–87. [PubMed: 19384675]
5. Abraham WT, Adamson PB, Bourge RC, Aaron MF, Costanzo MR, Stevenson LW, Strickland W, Neelagaru S, Raval N, Krueger S, Weiner S, Shavelle D, Jeffries B, Yadav JS. CHAMPION Trial Study Group. Wireless pulmonary artery haemodynamic monitoring in chronic heart failure: a randomized controlled trial. Lancet. 2011; 377:658–666. [PubMed: 21315441]
6. Vivo RP, Krim SR, Perez J, Inklab M, Tenner T Jr, Hodgson J. Digoxin: current use and approach to toxicity. Am J Med Sci. 2008; 336:423–428. [PubMed: 19011400]
7. Pervaiz MH, Dickinson MG, Yamani M. Is digoxin a drug of the past? Cleve Clin J Med. 2006; 73:821–824. 829–832. [PubMed: 16970134]
8. Goldberger ZD, Goldberger AL. Therapeutic ranges of serum digoxin concentrations in patients with heart failure. Am J Cardiol. 2012; 12:1818–1821. [PubMed: 22502901]
9. US Consumer Product Safety Commission. National Electronic Injury Surveillance System All Injury Program Sample Design and Implementation. Washington, DC: US Consumer Product Safety Commission; 2002.
10. Jhung MA, Budnitz DS, Mendelsohn AB, Weidenbach KN, Nelson TD, Pollock DA. Evaluation and overview of the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance Project (NEISS-CADES). Med Care. 2007; 45:S96–S102. [PubMed: 17909391]
11. Budnitz DS, Pollock DA, Weidenbach KN, Mendelsohn AB, Schroeder TJ, Annest JL. National surveillance of emergency department visits for outpatient adverse drug events. JAMA. 2006; 296:1858–1866. [PubMed: 17047216]

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12. Bousquet C, Lagier G, Louët AL, Le Beller C, Venot A, Jaulent MC. Appraisal of the MedDRA conceptual structure for describing and grouping adverse drug reactions. Drug Safety. 2005; 28:19–34. [PubMed: 15649103]
13. National Center for Health Statistics. [Accessed August 27, 2013] NAMCS/NHAMCS questionnaires, datasets, and related documentation. Available at: http://www.cdc.gov/nchs/ahcd/ahcd_questionnaires.htm#public_use
14. National Center for Health Statistics. [Accessed August 27, 2013] Dataset documentation: National Ambulatory Medical Care. Available at: ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NAMCS/
15. National Center for Health Statistics. [Accessed August 27, 2013] Dataset documentation: National Hospital Ambulatory Medical Care Survey. Available at: ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Dataset_Documentation/NHAMCS/
16. National Center for Health Statistics. [Accessed August 27, 2013] Trend analysis using NAMCS and NHAMCS drug data. Available at: http://www.cdc.gov/nchs/ahcd/trend_analysis.htm
17. National Center for Health Statistics. [Accessed August 27, 2013] NAMCS/NHAMCS Estimation Procedures. Available at: http://www.cdc.gov/nchs/ahcd/ahcd_estimation_procedures.htm
18. Kish, L. Survey Sampling. New York: Wiley Interscience; 1995.
19. Kegler SR. Applying the compound poisson process model to the reporting of injury-related mortality rates. Epidemiol Perspect and Innov. 2007; 4:1.
20. Top 200 Drugs of 1997: IMS analysis describes major market shifts. Pharmacy Times. 1998; 64:31–49.
21. The Digitalis Investigation Group. The effect of digoxin on mortality and morbidity in patients with heart failure. N Engl J Med. 1997; 336:525–533. [PubMed: 9036306]
22. Packer M. End of the oldest controversy in medicine—are we ready to conclude the debate on digitalis? N Engl J Med. 1997; 336:575–576. [PubMed: 9023096]
23. Caccamo MA, Eckman PM. Pharmacologic therapy for New York Heart Association Class IV heart failure. Congest Heart Fail. 2011; 17:213–219. [PubMed: 21906245]
24. Haynes K, Heitjan D, Kanetsky P, Hennessy S. Declining public health burden of digoxin toxicity from 1991 to 2004. Clin Pharmacol Ther. 2008; 84:90–94. [PubMed: 18091761]
25. Hussain Z, Swindle J, Hauptman PJ. Digoxin use and digoxin toxicity in the post-DIG trial era. J Card Fail. 2006; 12:343–346. [PubMed: 16762795]
26. Adams KF Jr, Patterson JH, Gattis WA, O'Connor CM, Lee CR, Schwartz TA, Gheorghiade M. Relationship of serum digoxin concentration to mortality and morbidity in women in the digitalis investigation group trial: a retrospective analysis. J Am Coll Cardiol. 2005; 46:497–504. [PubMed: 16053964]
27. Rathore SS, Wang Y, Krumholz HM. Sex-based differences in the effect of digoxin for the treatment of heart failure. N Engl J Med. 2002; 347:1403–1411. [PubMed: 12409542]
28. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med. 2011; 365:2002–2012. [PubMed: 22111719]
29. Currie GM, Wheat JM, Kiat H. Pharmacokinetic considerations for digoxin in older people. Open Cardiovasc Med J. 2011; 5:130–135. [PubMed: 21769303]
30. Hanratty CG, McGlinchey P, Johnston GD, Passmore AP. Differential pharmacokinetics of digoxin in elderly patients. Drugs Aging. 2000; 17:353–362. [PubMed: 11190416]
31. Ahmed A, Waagstein F, Pitt B, White M, Zannad F, Young JB, Rahimtoola SH. Digitalis investigation group. Effectiveness of digoxin in reducing one-year mortality in chronic heart failure in the Digitalis Investigation Group trial. Am J Cardiol. 2009; 103:82–87. [PubMed: 19101235]
32. Meyer P, White M, Mujib M, Nozza A, Love TE, Aban I, Young JB, Wehrmacher WH, Ahmed A. Digoxin and reduction of heart failure hospitalization in chronic systolic and diastolic heart failure. Am J Cardiol. 2008; 102:1681–6. [PubMed: 19064024]
33. Bourge RC, Fleg JL, Fonarow GC, Cleland JG, McMurray JJ, van Veldhuisen DJ, Gheorghiade M, Patel K, Aban IB, Allman RM, White-Williams C, White M, Filippatos GS, Anker SD, Ahmed A. Digoxin reduces 30-day all-cause hospital admission in older patients with chronic systolic heart failure. Am J Med. 2013; 126:701–708. [PubMed: 23490060]

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34. Gheorghiade M, Patel K, Filippatos G, Anker SD, van Veldhuisen DJ, Cleland JG, Metra M, Aban IB, Greene SJ, Adams KF, McMurray JJ, Ahmed A. Effect of oral digoxin in high-risk heart failure patients: a pre-specific subgroup analysis of the DIG trial. Eur J Heart Fail. 2013; 15:551–9. [PubMed: 23355060]

35. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, Fonarow GC, Geraci SA, Horwich T, Januzzi JL, Johnson MR, Kasper EK, Levy WC, Masoudi FA, McBride PE, McMurray JJ, Mitchell JE, Peterson PN, Riegel B, Sam F, Stevenson LW, Tang WH, Tsai EJ, Wilkoff BL. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Circulation. 2013; 128:e240–e327. [PubMed: 23741058]

36. Hauptman PJ, McCann P, Romero JM, Mayo M. Reference laboratory values for digoxin following publication of Digitalis Investigation Group (DIG) trial data. JAMA Int Med. 2013; 173:1552–1554.

37. Haynes K, Hennessy S, Localio AR, Cohen A, Leonard CE, Kimmel SE, Feldman HI, Strom BL, Metlay JP. Increased risk of digoxin toxicity following hospitalization. Pharmacoepidemiol Drug Saf. 2009; 18:28–35. [PubMed: 19040200]

38. Bradley EH, Curry L, Horwitz LI, Sipsma H, Thompson JW, Elma M, Walsh MN, Krumholz HM. Contemporary evidence about hospital strategies for reducing 30-day readmissions: a national study. J Am Coll Cardiol. 2012; 60:607–614. [PubMed: 22818070]

39. Aarnoudse AL, Dieleman JP, Stricker BH. Age- and gender-specific incidence of hospitalisation for digoxin intoxication. Drug Saf. 2007; 30:431–436. [PubMed: 17472421]

40. Miura T, Kojima R, Sugiura Y, Mizutani M, Takatsu F, Suzuki Y. Effect of aging on the incidence of digoxin toxicity. Ann Pharmacother. 2000; 34:427–432. [PubMed: 10772425]

41. Francis GS. The contemporary use of digoxin for the treatment of heart failure. Circ Heart Fail. 2008; 1:208–209. [PubMed: 19808292]

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Table 1

Number of Cases and National Estimates of Emergency Department Visits for Digoxin Toxicity Among Persons Age 40 Years or Older, by Patient Age and Sex, and Year of Visit—United States, 2005–2010

Case Characteristics	Emergency Department Visits				Proportion of ED Visits Resulting in Hospitalization	
		Annual National Estimate			Annual National Estimate	
	Cases, No.	No.	%	95% Confidence Interval	%	95% Confidence Interval
Age (years)						
40–69	98	1,076	20.9	15.3–26.5	79.0	69.3–88.7
70–84	200	2,339	45.4	37.0–53.7	77.4	70.5–84.3
≥85	143	1,741	33.8	24.7–42.8	80.5	72.6–88.5
Sex						
Male	143	1,662	32.2	62.9–72.6	75.2	68.4–82.0
Female	298	3,493	67.8	27.4–37.1	80.5	74.0–87.1
Year of ED Visit*						
2005–2006	139	5,163	33.4	25.4–41.3	77.7	69.3–86.1
2007–2008	159	5,274	34.1	26.1–42.1	76.4	69.9–82.8
2009–2010	143	5,031	32.5	20.6–44.5	82.5	72.5–92.5
Total	**441**	5,156	-	-	78.8	73.5–84.1

ED indicates emergency department.

Case counts and estimates from the National Electronic Injury Surveillance System - Cooperative Adverse Drug Event Surveillance project, 2005–2010, Centers for Disease Control and Prevention.

*For “Year of ED Visit”, percent (%) and corresponding 95% confidence intervals are out of ED visits for digoxin toxicity during the entire 2005–2010 time period.

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Table 2

Number of Cases and National Estimates of Emergency Department Visits for Digoxin Toxicity Among Persons Age 40 Years or Older, by Serum Digoxin Levels Reported—United States, 2005–2010

Serum Digoxin Level Reported (n=251 cases)*	Emergency Department Visits		
		Annual National Estimate	
	Cases, No.	%	95% Confidence Interval
Level (ng/mL)			
0.0–0.9	3	-	-
1.0–1.9	8	-	-
2.0–2.9	121	54.2	43.8–64.5
3.0–3.9	87	28.5	19.7–37.4
≥4.0	32	12.5	6.9–18.1

Case counts and estimates from the National Electronic Injury Surveillance System - Cooperative Adverse Drug Event Surveillance project, 2005–2010, Centers for Disease Control and Prevention. Estimates with case count <20 or coefficient of variation >30% are considered unstable and are not shown (-).

*Data are shown only for cases where a serum digoxin level was documented (251 of 441 cases).

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Table 3

Number of Cases and National Estimates of Emergency Department Visits for Digoxin Toxicity Among Persons Age 40 Years or Older, by Clinical Manifestation—United States, 2005–2010

Clinical Manifestation (n=365)*	Emergency Department Visits		
		Annual National Estimate	
	Cases, No.	%	95% Confidence Interval
Category†			
Central nervous system	**84**	**25.2**	17.4–33.1
Altered mental status	63	17.2	11.1–23.4
Other central nervous system manifestation	21	8.1	4.7–11.5
Cardiovascular	**152**	**44.5**	37.3–51.7
Symptomatic disturbance in rate/rhythm‡	41	10.6	6.4–14.9
Syncope	44	12.5	7.4–17.5
Dyspnea	35	11.9	6.5–17.2
Other cardiovascular system manifestation	32	9.5	6.3–12.8
Gastrointestinal	**43**	**9.7**	5.8–13.5
Other symptoms	**39**	**11.9**	8.0–15.8
Only “elevated digoxin level” or “digoxin toxicity” recorded§	**47**	-	-

Case counts and estimates from the National Electronic Injury Surveillance System - Cooperative Adverse Drug Event Surveillance project, 2005–2010, Centers for Disease Control and Prevention. Estimates with case count <20 or coefficient of variation >30% are considered unstable and are not shown (−).

*Data are shown only for cases where digoxin was the only offending drug implicated in the ED visit and at least one clinical symptom was provided (365 of 441 cases).

†Categories are mutually exclusive and were assigned hierarchically. For example, a case where a patient presented with both confusion and bradycardia would be categorized under the category “Central nervous system.”

‡Includes symptomatic bradycardia/bradyarrhythmias (29 cases), palpitations without rate/rhythm specified (6 cases), tachycardia/tachyarrhythmia (4 cases), and rate disturbance not otherwise specified (2 cases)

§Presenting clinical symptoms not recorded for these cases.

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Table 4

Rates of Emergency Department Visits for Digoxin Toxicity Among Persons Age 40 Years or Older Per Outpatient Prescription Visits, by Patient Age and Sex, and Year of Visit—United States, 2005–2010

	Annual National Estimate, No.		ED Visits per 10,000 OPVs	
	ED Visits	OPVs	Rate	95% Confidence Interval
Age (yrs)				
40–69	1,076	2,969,993	3.6	1.5–5.8
70–84	2,339	4,685,053	5.0	2.0–8.0
≥85	1,741	1,605,531	10.8	6.1–15.6
Sex				
Male	1,662	4,803,080	3.5	1.5–5.4
Female	3,493	4,457,497	7.8	4.2–11.5
Year of ED Visit				
2005–2006	5,163	9,441,084	5.5	2.1–8.8
2007–2008	5,275	9,183,850	5.7	2.6–8.9
2009–2010	5,031	9,156,796	5.5	2.4–8.6

ED indicates emergency department; OPV, Outpatient Prescription Visits.

ED visit estimates from the National Electronic Injury Surveillance System - Cooperative Adverse Drug Event Surveillance project, 2005–2010, Centers for Disease Control and Prevention. OPV estimates from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey, 2005–2010, Centers for Disease Control and Prevention.