

Monitoring of Drugs With a Narrow Therapeutic Range in Ambulatory Care

Marsha A. Raebel, PharmD; Nikki M. Carroll, MS; Susan E. Andrade, ScD; Elizabeth A. Chester, PharmD; Jennifer Elston Lafata, PhD; Adrienne Feldstein, MD; Margaret J. Gunter, PhD; Winnie W. Nelson, PharmD; Steven R. Simon, MD, MPH; K. Arnold Chan, MD, ScD; Robert L. Davis, MD, MPH; and Richard Platt, MD

Objectives: To describe the proportion of patients receiving drugs with a narrow therapeutic range who lacked serum drug concentration monitoring during a 1-year period of therapy and to identify patient characteristics associated with lack of monitoring.

Study Design: Retrospective cohort.

Methods: Ambulatory patients (n = 17 748) at 10 health maintenance organizations who were receiving ongoing continuous drug therapy with digoxin, carbamazepine, divalproex sodium, lithium carbonate, lithium citrate, phenobarbital sodium, phenytoin, phenytoin sodium, primidone, quinidine gluconate, quinidine sulfate, procainamide hydrochloride, theophylline, theophylline sodium glycinate, tacrolimus, or cyclosporine for at least 12 months between January 1, 1999, and June 30, 2001, were identified. Serum drug concentration monitoring was assessed from administrative data and from medical record data.

Results: Fifty percent or more of patients receiving digoxin, theophylline, procainamide, quinidine, or primidone were not monitored, and 25% to 50% of patients receiving divalproex, carbamazepine, phenobarbital, phenytoin, or tacrolimus were not monitored. Younger age was associated with lack of monitoring for patients prescribed digoxin (adjusted odds ratio, 1.86; 95% confidence interval, 1.39-2.48) and theophylline (adjusted odds ratio, 1.58; 95% confidence interval, 1.23-2.04), while older age was associated with lack of monitoring for patients prescribed carbamazepine (adjusted odds ratio, 0.59; 95% confidence interval, 0.44-0.80) and divalproex (adjusted odds ratio, 0.50; 95% confidence interval, 0.38-0.66). Patients with fewer outpatient visits were also less likely to be monitored ($P < .001$).

Conclusions: A substantial proportion of ambulatory patients receiving drugs with narrow intervals between doses resulting in beneficial and adverse effects did not have serum drug concentration monitoring during 1 year of use. Clinical implications of this finding need to be evaluated.

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The goal of therapeutic drug monitoring is to guide dosing by means of drug concentration measurements. Therapeutic drug monitoring is useful for drugs that lack correlation between dose and pharmacodynamic properties, for drugs that have nonlinear correlations between dose and effect, and for drugs that have a narrow therapeutic range (NTR) between the dose necessary to achieve beneficial effects and the dose that causes serious adverse effects when there is a direct

concentration–effect relationship. Individualizing the drug dosage and the dosing interval can minimize the toxicity and maximize the therapeutic benefit of NTR drugs.¹ The first step toward individualizing therapy is to evaluate the drug concentration in the body, often from a serum sample. Although there is controversy about whether monitoring should be routine, as well as about the frequency and timing of therapeutic drug monitoring to maximize beneficial drug effects,²⁻⁴ there is general agreement that therapeutic drug monitoring is useful in avoiding drug toxicity. For example, drug concentration monitoring is recommended as a quality-of-care indicator for patients taking phenytoin, phenobarbital, divalproex sodium, and carbamazepine.^{5,6} Concentration monitoring of many NTR drugs is routinely available at healthcare laboratories, but little is known about the frequency of monitoring among ambulatory patients.

We undertook a study to assess drug concentration monitoring in ambulatory patients receiving NTR drugs. The objectives of this study were to describe the proportion of patients dispensed NTR drugs who did not have

From the Clinical Research Unit (MAR, NMC) and Pharmacy Department (EAC), Kaiser Permanente of Colorado, and University of Colorado School of Pharmacy (MAR, EAC), Denver; Meyers Primary Care Institute, Fallon Foundation, and University of Massachusetts Medical School, Worcester (SEA), and Harvard Pilgrim Health Care and Harvard Medical School (SRS, RP) and Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School (KAC, RP), Boston; Henry Ford Health System, Detroit, Mich (JEL); Kaiser Permanente Northwest Center for Health Research and Oregon Health Sciences University, Portland (AF); Lovelace Clinic Foundation, Albuquerque, NM (MJG); HealthPartners Research Foundation, Minneapolis, Minn (WWN); and Group Health Cooperative Center for Health Studies and Department of Epidemiology, University of Washington, Seattle (RLD).

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Address correspondence to: Marsha A. Raebel, PharmD, Clinical Research Unit, Kaiser Permanente of Colorado, PO Box 378066, Denver, CO 80237-8066. E-mail: marsha.a.raebel@kp.org.

drug concentration monitoring during a 1-year therapy period and to identify patient characteristics associated with lack of monitoring. The results of this study provide information to guide thoughtful establishment of quality-of-care indicators related to NTR drug monitoring in ambulatory patients.

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METHODS

Study Population and Design

This retrospective cohort study of ongoing NTR drug therapy was designed to assess rates and correlates of serum drug concentration monitoring among ambulatory members of 10 health maintenance organizations in geographically diverse US locations. We studied monitoring practices for the following NTR drugs: carbamazepine, cyclosporine, digoxin, lithium, phenytoin, phenobarbital, primidone, procainamide hydrochloride, quinidine, tacrolimus, theophylline, and divalproex (valproic acid). The first study objective was to assess the proportion of ambulatory patients receiving continuous ongoing therapy with an NTR drug who did not have at least 1 drug serum concentration monitored within a 1-year period. The second study objective was to evaluate possible associations between lack of NTR drug monitoring and patient age, sex, outpatient visits, chronic diseases, diagnoses, selected socioeconomic status variables, and hospitalizations. Finally, the accuracy of using automated data in identifying drug concentration monitoring was assessed.

The participating organizations comprise the HMO Research Network Center for Education and Research in Therapeutics, which has been described elsewhere.⁷ In brief, the center includes staff, group, network, independent practice association, and mixed-model health maintenance organizations that serve racially and ethnically diverse populations and in 2000 provided health-care for approximately 7 million people in more than 1000 locations. The institutional review board of each participating organization approved this study.

The study sample was drawn from a data set of 2 020 037 individuals, consisting of approximately 200 000 randomly selected health plan members from each of the 10 organizations. The sampling scheme and demographic distribution of this population have been previously described.⁸ We identified patients who received an NTR drug of interest between January 1, 1999, and May 31, 2000, and who had continuous health plan membership with pharmacy benefits during the study period, disregarding gaps of less than 60 days. The study sample was limited to prevalent users who had continued drug dispensings of and ongoing therapy with an NTR drug. To avoid inadvertent inclusion of new

drug users in the study cohort, prevalent ongoing therapy was defined as beginning with the second dispensing of that drug in the data set and continuing from the second dispensing date for 12 months or longer. Continued dispensings were present when no interval between prescription refills was greater than the dispensed days' supply plus 1.5 times the dispensed days' supply. A dispensing gap was ignored if it was less than 1.5 times the dispensed days' supply. For example, a patient dispensed a 30-day supply met the criterion of continued dispensings if no more than 75 days (30 days + [1.5 × 30 days]) elapsed between the date of one dispensing and the date of the subsequent dispensing. NTR drug dispensings were identified using National Drug Code numbers. For all eligible patients, we used automated health plan data to ascertain dates of health plan membership and drug dispensings.

Identification and Categorization of Drug Concentration Monitoring

Lack of laboratory monitoring was defined as failure to perform drug concentration monitoring within the 1-year period of ongoing therapy, allowing up to a 1-month grace period (ie, monitoring within 13 months was considered as monitoring within 1 year). To accommodate patients entering the cohort between January 1, 1999, and May 31, 2000, monitoring data were collected for January 1, 1999, through June 30, 2001. Whether the laboratory test was performed was assessed from the presence of an administrative claim for the test. The laboratory test date was the date the test was performed or the result was reported. Laboratory test codes were defined at each site according to that site's method of coding the test (eg, *Current Procedural Terminology* codes). One site was unable to contribute drug concentration monitoring data for carbamazepine, digoxin, cyclosporine, and phenytoin.

Medical records were randomly selected for review to assess the accuracy of administrative data. Because of resource limitations, this review included medical records of patients dispensed cyclosporine, digoxin, and carbamazepine. Medical record abstraction was considered the gold standard, and abstraction data were compared with administrative data to determine the sensitivity, specificity, positive predictive value, and negative predictive value of administrative information about drug concentration monitoring.

Identification and Definition of Other Patient Characteristics

The health maintenance organization automated databases were used to identify the patient age (on the date of the first NTR drug dispensing), sex, outpatient

visits, chronic diseases, diagnoses, and hospitalizations. The presence of specific chronic diseases was determined using the Chronic Disease Score method by Clark et al.⁹ To evaluate characteristics that predicted lack of monitoring, hospitalizations and outpatient visits that occurred within 6 months before the study period were identified. Outpatient visits include clinic appointments, visits for laboratory testing only, and emergency department visits. Geocoding was used to provide surrogate patient-level measures of socioeconomic status. Residential street address was combined with census-block level data from the 2000 US Census data to construct proxies of patient race, education, and poverty.¹⁰

Statistical Analysis

The number of unique patient–drug therapy combinations and the number of patients were tabulated. Descriptive statistics were computed to characterize patients, drug dispensings, and drug concentration monitoring for each drug cohort. The proportions of patients taking each NTR drug who received drug concentration monitoring and those who did not receive drug concentration monitoring were tabulated overall and by health plan, age group, sex, outpatient visits, hospitalizations, Chronic Disease Score, race, education, and poverty categories. Statistical significance of differences was tested using the Wilcoxon rank sum test or the χ^2 test.

The association between patient characteristics and drug concentration monitoring was evaluated using generalized estimating equation logistic regression modeling, with site as a cluster variable.¹¹ The initial generalized estimating equation model for each drug included the following variables with $P < .05$ in the univariate analysis: age group, sex, outpatient visits (in increments of 5 visits), hospitalizations, the presence or absence of selected diagnoses, and the 3 linear socioeconomic status variables. The Chronic Disease Score was not included in any of the initial models because it was correlated with outpatient visits. We used the backward selection method for all generalized estimating equation models. Customary residual and effect statistics were examined to assess model fit and to evaluate outliers. Analyses were performed using SAS version 8.2 or 9.1 (SAS Institute Inc, Cary, NC).

RESULTS

Almost 18 000 patients ($n = 17\,748$) met the eligibility criteria for the study; these patients represented 18 821 individual patient–drug therapy combinations

(5.7% of patients received > 1 study drug). Patient characteristics are given in **Table 1**. Patients prescribed digoxin ($n = 7153$), divalproex ($n = 2209$), carbamazepine ($n = 1876$), phenytoin ($n = 2232$), theophylline ($n = 2195$), and lithium ($n = 1487$) accounted for 91% of the study patients. The median number of drug dispensings during 1 year ranged from 6 for digoxin to 12 for cyclosporine (data not shown).

The proportions of patients who were not monitored were low (14%) for cyclosporine and lithium (**Figure**). However, for patients prescribed digoxin, theophylline, procainamide, quinidine, or primidone, 50% or more were not monitored. Between 25% and 50% of patients prescribed divalproex, carbamazepine, phenobarbital, phenytoin, or tacrolimus did not have a serum concentration evaluated within the 1-year period.

Nine participating sites contributed data for all study drugs. At 8 of these sites, 36% to 48% of patients lacked monitoring; at the 9th site, 62% of patients were not monitored. Because the 10th site did not contribute data for 4 NTR drugs, the percentage of patients without monitoring for all NTR study drugs could not be determined.

A consistent association between patients' median age and lack of monitoring was not observed in the univariate analysis. Patients prescribed digoxin (77 vs 74 years, $P < .001$), procainamide (75 vs 71 years, $P = .02$), or theophylline (65 vs 61 years, $P < .001$) who were less likely to be monitored were younger, while patients prescribed carbamazepine (45 vs 49 years, $P < .001$), divalproex (44 vs 47 years, $P < .001$), or primidone (55 vs 69 years, $P < .001$) who were less likely to be monitored were older. For all study drugs, patients who were less likely to be monitored had a lower median number of outpatient visits. This difference was significant for digoxin (10 vs 8 visits, $P < .001$), theophylline (6 vs 4 visits, $P < .001$), divalproex (7 vs 5 visits, $P < .001$), carbamazepine (6 vs 4 visits, $P < .001$), phenytoin (5 vs 3 visits, $P < .001$), lithium (8 vs 5 visits, $P < .001$), and phenobarbital (5 vs 4 visits, $P = .01$).

There was a statistically significant ($P < .001$) difference (but unlikely a clinically significant difference) in the median percentages of monitored patients who had at least a high school education (89% [5th-95th percentiles, 64%-98%]) compared with patients who had at least a high school education who lacked monitoring (88% [5th-95th percentiles, 62%-98%]). Because patient race was correlated with poverty and with education (Spearman rank correlation coefficient [ρ] range for race and poverty for individual drugs, -0.43 to -0.53 ; and ρ range for race and education for individual drugs, 0.36 - 0.45) and because poverty and education were correlated (ρ range for poverty and education for individual

drugs, -0.31 to -0.63), race and poverty were not considered further in the analysis.

Logistic regression analysis was used to evaluate associations between patient characteristics and lack of monitoring for the 6 prescribed drugs that accounted for 91% of the study patients (Table 2). When other characteristics were adjusted for, the patient characteristics most consistently associated with monitoring status continued to be age and outpatient visits, while the numbers of chronic diseases and recent hospitalizations were not associated with lack of monitoring for any of these drugs. Younger patients prescribed digoxin were more likely than the oldest patients prescribed digoxin to lack monitoring. Other factors associated with monitoring status of digoxin were female sex, the number of outpatient visits, and a diagnosis of arrhythmia or heart failure. These factors were associated with a lower likelihood of lacking monitoring (ie, patients with these factors were more likely to be monitored).

For patients prescribed theophylline, those in the youngest age group were more likely to lack monitoring than those in the oldest age group (Table 2).

Table 1. Characteristics of Ambulatory Patients Prescribed Drugs With a Narrow Therapeutic Range*

Drug	No. of Patients Prescribed Drug (n = 18 821) [†]	Median Age, y	Female Sex, %	No. of Chronic Diseases	Hospitalizations, % [‡]	No. of Outpatient Visits [‡]
Cardiovascular						
Digoxin	7153	75 (51-89)	51	5 (2-8)	1625 (23)	9 (1-26)
Procainamide	59	74 (49-87)	44	4 (1-9)	12 (20)	7 (1-26)
Quinidine	180	74 (54-87)	39	4 (1-8)	24 (13)	7 (0-22)
Immunosuppressive						
Cyclosporine	350	51 (29-69)	39	6 (2-11)	86 (25)	11 (2-36)
Tacrolimus	132	49 (14-70)	46	7 (2-11)	43 (33)	13 (1-40)
Mental health and antiepileptic						
Carbamazepine	1876	47 (11-80)	58	2 (1-7)	218 (12)	5 (0-22)
Lithium	1487	50 (19-77)	60	4 (1-8)	163 (11)	7 (1-28)
Phenobarbital	629	54 (18-83)	56	3 (1-7)	94 (15)	5 (0-22)
Phenytoin	2232	56 (27-84)	44	2 (1-7)	341 (15)	4 (0-21)
Primidone	319	65 (42-86)	54	4 (1-9)	49 (15)	7 (0-25)
Divalproex	2209	45 (11-75)	54	3 (1-8)	294 (13)	7 (1-26)
Other						
Theophylline	2195	63 (36-83)	57	4 (1-8)	380 (17)	5 (0-22)

*Data are given as median (5th-95th percentiles) unless otherwise indicated.

[†]The total number of patients (n = 17 748) is less than the number of patient-drug therapy combinations (n = 18 821) because 5.7% of the 17 748 unique patients received more than 1 of the drugs with a narrow therapeutic range included in the study.

[‡]Unique patients hospitalized or unique outpatient visits within 6 months before the evaluation period.

Figure. Percentages of Ambulatory Patients Without Serum Concentration Monitoring of Drugs With a Narrow Therapeutic Range

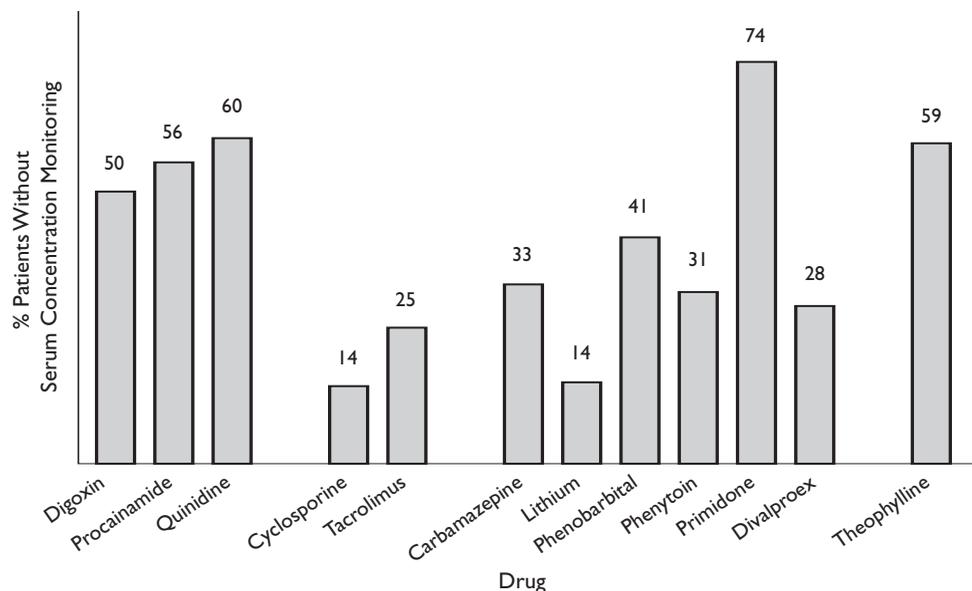


Table 2. Characteristics Associated With Absence of Drug Concentration Monitoring for Patients Prescribed Digoxin, Carbamazepine, Divalproex, Lithium, Phenytoin, and Theophylline*

Characteristic	Unadjusted Odds Ratio	Adjusted Odds Ratio (95% Confidence Interval)
Digoxin		
Sex, male sex as referent	0.81	0.83 (0.76-0.92)
Age group		
Quartile 1	2.09	1.86 (1.39-2.48)
Quartile 2	1.54	1.38 (1.20-1.58)
Quartile 3	1.44	1.38 (1.24-1.54)
Quartile 4, oldest	1.00 (Referent)	1.00 (Referent)
Outpatient visits, increment of 5 visits	0.87	0.90 (0.87-0.93)
Diagnosis [†]		
Arrhythmia	0.59	0.68 (0.60-0.76)
Heart failure	0.71	0.77 (0.70-0.85)
Carbamazepine		
Age group		
Quartile 1	0.58	0.59 (0.44-0.80)
Quartile 2	0.84	0.85 (0.64-1.13)
Quartile 3	0.94	0.93 (0.70-1.23)
Quartile 4, oldest	1.00 (Referent)	1.00 (Referent)
Outpatient visits, increment of 5 visits	0.79	0.79 (0.72-0.86)
Diagnosis [†]		
Seizures	0.56	0.52 (0.42-0.65)
Mental health	0.60	0.61 (0.48-0.77)
Divalproex		
Age group		
Quartile 1	0.51	0.50 (0.38-0.66)
Quartile 2	0.82	0.77 (0.59-1.00)
Quartile 3	0.77	0.74 (0.57-0.97)
Quartile 4, oldest	1.00 (Referent)	1.00 (Referent)
Outpatient visits, increment of 5 visits	0.88	0.90 (0.84-0.96)
Diagnosis [†]		
Seizures	0.71	0.45 (0.33-0.61)
Mental health	0.66	0.44 (0.34-0.58)
Seizure-x-mental health diagnoses interaction		0.34 (0.12-0.98)
Lithium		
Sex, male sex as referent	0.62	0.71 (0.55-0.91)
Outpatient visits, increment of 5 visits	0.78	0.77 (0.62-0.96)
Phenytoin		
Outpatient visits, increment of 5 visits	0.76	0.75 (0.69-0.81)
Theophylline		
Age group		
Quartile 1	1.81	1.58 (1.23-2.04)
Quartile 2	1.20	1.10 (0.86-1.41)
Quartile 3	0.96	0.94 (0.74-1.20)
Quartile 4, oldest	1.00 (Referent)	1.00 (Referent)
Outpatient visits, increment of 5 visits	0.89	0.92 (0.87-0.97)
Diagnosis of chronic obstructive pulmonary disease [†]	0.67	0.81 (0.67-0.98)

Fewer outpatient visits and a diagnosis of chronic obstructive pulmonary disease were associated with lacking theophylline monitoring.

In contrast to the relationship between younger patient age and the presence of monitoring that was observed for digoxin and theophylline, patients prescribed carbamazepine or divalproex who were in the oldest age group were more likely to lack monitoring (Table 2). For carbamazepine and divalproex, a seizure diagnosis or a mental health diagnosis was associated with a lower likelihood of lacking monitoring, as was an increasing number of outpatient visits.

Because patients prescribed carbamazepine or divalproex who did not have a seizure diagnosis or a mental health diagnosis had characteristics that were different from those of individuals with these diagnoses (Table 3), we analyzed these patient groups separately. For carbamazepine, the association between being in the oldest age group and having a lower likelihood of monitoring was significant in patients with a mental health diagnosis (odds ratio, 0.24; 95% confidence interval, 0.11-0.54 for the youngest age group). Similarly, for divalproex, the association between being in the oldest age group and having a lower likelihood of monitoring was significant in patients with a mental health diagnosis (odds ratio, 0.47; 95% confidence interval, 0.32-0.69 for the youngest age group; and odds ratio, 0.53; 95% confidence interval, 0.36-0.77 for the second youngest age group), as well as for the youngest age group of patients who had neither a seizure diagnosis nor a mental health diagnosis (odds ratio, 0.42; 95% confidence interval, 0.22-0.83 for the youngest age group).

*One patient who was an outlier was removed before model evaluations for digoxin, carbamazepine, lithium, and phenytoin. *Quartile 1:* digoxin, 1 to 48 years; carbamazepine, 2 to 33 years; divalproex, 2 to 28 years; and theophylline, 8 to 53 years. *Quartile 2:* digoxin, 49 to 63 years; carbamazepine, 34 to 47 years; divalproex, 29 to 45 years; and theophylline, 54 to 63 years. *Quartile 3:* digoxin, 64 to 76 years; carbamazepine, 48 to 59 years; divalproex, 46 to 55 years; and theophylline, 64 to 73 years. *Quartile 4:* digoxin, 77 years or older; carbamazepine, 60 years or older; divalproex, 56 years or older; and theophylline, 74 years or older. Outpatient visits comprise unique visits within 6 months before the evaluation period.
[†]Reference group included all patients prescribed the drug who did not have that diagnosis.

Table 3. Characteristics of Patients Prescribed Carbamazepine and Divalproex

Diagnosis	No. of Patients Prescribed the Drug	No. of Patients Without Monitoring, %	Median Age, y	Hospitalizations, %*	Median No. (5th-95th Percentiles) of Outpatient Visits*	Median No. (5th-95th Percentiles) of Drug Dispensings Within 1 Year
Carbamazepine	1876	613 (33)				
Seizure indication only	893	265 (30)	41	8	4 (0-15)	11 (4-16)
Mental health indication only	311	88 (28)	51	12	9 (1-29)	10 (4-16)
Both seizure and mental health indications	277	61 (22)	48	16	7 (1-27)	12 (5-17)
Neither seizure nor mental health indication	395	199 (50)	54	3	3 (0-16)	7 (4-14)
Divalproex	2209	628 (28)				
Seizure indication only	521	134 (26)	30	8	3 (0-19)	11 (4-16)
Mental health indication only	1112	292 (26)	47	16	9 (1-28)	12 (5-15)
Both seizure and mental health indications	262	54 (21)	44	15	9 (1-33)	12 (5-15)
Neither seizure nor mental health indication	314	148 (47)	47	2	4 (0-17)	8 (4-16)

*Unique patients hospitalized or unique outpatient visits within 6 months before the evaluation period.

The sensitivity of claims data compared with medical record data for drug concentration monitoring was excellent (89% [47/53] for digoxin, 93% [70/75] for carbamazepine, and 95% [63/66] for cyclosporine). The specificity varied (94% [34/36] for digoxin, 78% [14/18] for carbamazepine, and 50% [11/22] for cyclosporine). The positive predictive value, the percentage of patients who had serum drug concentration monitoring according to administrative data that was also documented in medical records, was high (96% [47/49] for digoxin, 81% [60/74] for carbamazepine, and 85% [63/74] for cyclosporine). The negative predictive value, the percentage of patients who did not have serum drug concentration monitoring according to administrative data that was also not documented in medical records, was good (85% [34/40] for digoxin, 74% [14/19] for carbamazepine, and 79% [11/14] for cyclosporine).

DISCUSSION

Surprisingly high proportions of patients prescribed digoxin, theophylline, phenytoin, carbamazepine, procainamide, quinidine, primidone, divalproex, and phenobarbital (all medications with an NTR) do not have drug concentrations monitored at least yearly. In contrast, lithium and cyclosporine drug serum concentrations were monitored in most patients. Monitoring is

recommended for these drugs because life-threatening toxicity can result when concentrations are elevated, therapeutic efficacy can be lost when concentrations are low, and correlations between drug dosages administered and concentrations achieved can be poor.

The most consistent patient characteristic associated with lack of monitoring was a low number of outpatient visits, a finding that is intuitive. For example, it is feasible that the high monitoring rate observed with cyclosporine is related to the fact that patients prescribed this drug have a high number of outpatient visits (median, 11 visits in a 6-month period) (Table 1).

Age was also often associated with lack of monitoring, but the association between age and monitoring varied by drug, with younger age being a predictor of lack of monitoring for patients prescribed digoxin and theophylline, and with older age being a predictor of lack of monitoring for patients prescribed carbamazepine and divalproex. The absence of a specific seizure diagnosis or mental health diagnosis for patients prescribed carbamazepine or divalproex increased the risk for lack of monitoring, as did the absence of an arrhythmia or heart failure diagnosis for patients prescribed digoxin and the absence of a chronic obstructive pulmonary disease diagnosis for patients prescribed theophylline.

Dosages of digoxin used to manage arrhythmias are often higher than dosages used to manage heart failure. Therefore, one could argue that monitoring is more

important for patients with arrhythmias because their risk of drug toxicity is greater. Yet, we found that the presence of either diagnosis was similarly protective against lack of monitoring (Table 2).

Patients prescribed carbamazepine who have seizures or a diagnosis such as bipolar disorder are at higher risk of drug toxicity because they are treated with higher drug dosages than patients prescribed carbamazepine for an indication such as trigeminal neuralgia.¹² It is feasible that clinicians are less concerned about efficacy and toxicity monitoring in patients prescribed carbamazepine for diagnoses other than seizures or bipolar disorders. The same rationale can be applied to patients prescribed divalproex who do not have a seizure diagnosis or a mental health diagnosis. Unfortunately, this study was not designed to evaluate whether a relationship existed between dosage and monitoring, nor was it designed to differentiate between drug concentration monitoring that was not performed because it was not ordered vs because the patient did not obtain the ordered test.

Our work did not evaluate the appropriateness of drug concentration measurements relative to the need, timing, and interpretation of monitoring.^{2-4,13-16} We acknowledge the importance of these factors in evaluating quality of care, but we believe that the information herein is meaningful even without information about the appropriateness of monitoring. Our findings document a widespread absence of drug concentration monitoring. Monitoring drug concentrations is viewed as a quality measure associated with avoiding preventable drug-related morbidity and disease exacerbations by organizations, including the National Committee for Quality Assurance in its Health Employer Information Data Set.^{5,6} The findings of our study can be used by organizations to improve rates of drug concentration monitoring through implementing guidelines that target the patient risk groups we identify herein as lacking monitoring.

We found good sensitivity, specificity, positive predictive value, and negative predictive value of administrative data compared with medical record data across the organizations that participated in this study. However, the generalizability of our results is limited by the fact that quality of care and the accuracy of administrative data vary across organizations. The quality of diagnostic and procedure coding depends on institutional experience with and emphasis on coding, as well as contractual arrangements between health plans and institutions.

There is a dearth of information about whether drug concentration monitoring reduces adverse outcomes in patients. The evidence we present herein of low rates of drug concentration monitoring should prompt investigations of clinical and economic outcomes in ambulatory patients who are prescribed NTR drugs and who do not receive drug concentration monitoring. Patient outcomes should be used to guide the refinement of existing NTR drug monitoring quality-of-care indicators in ambulatory patients.

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REFERENCES

1. Bauer LA. Clinical pharmacokinetics and pharmacodynamics. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. *Pharmacotherapy: A Pathophysiologic Approach*. 5th ed. New York, NY: McGraw-Hill; 2002:33-54.
2. Schoenenberger RA, Tanasijevic MJ, Jha A, Bates DW. Appropriateness of antiepileptic drug level monitoring. *JAMA*. 1995;274:1622-1626.
3. Pearce GA, Day DO. Compliance with criteria necessary for effective drug concentration monitoring. *Ther Drug Monit*. 1990;12:250-257.
4. McInnes GT. The value of therapeutic drug monitoring to the practicing physician: a hypothesis in need of testing. *Br J Clin Pharmacol*. 1989;27:281-284.
5. Mackinnon NJ, Hepler CD. Preventable drug-related morbidity in older adults, I: indicator development. *J Manag Care Pharm*. 2002;8:365-371.
6. National Committee for Quality Assurance. NCQA releases HEDIS 2006: new measures address overuse, follow-up [press release]. 2005. Available at: http://www.ncqa.org/communications/news/hedis_2006.htm. Accessed March 16, 2006.
7. Chan KA, Davis RL, Gunter MJ, et al. The HMO Research Network. In: Strom B, ed. *Pharmacoepidemiology*. 4th ed. Chichester, UK: John Wiley & Sons Inc; 2005: 261-269.
8. Chan KA; HMO Research Network CERTs Patient Safety Study Investigators. Development of a multipurpose data set to evaluate potential medication errors in ambulatory settings. In: *Advances in Patient Safety: From Research to Implementation*. Vol 2. Rockville, Md: Agency for Healthcare Research and Quality; February 2005. AHRQ Publication 050021 (1-4). Available at: <http://www.ahrq.gov/qual/advances/>. Accessed March 16, 2006.
9. Clark DO, Von Korff M, Saunders K, Baluch WM, Simon GE. A Chronic Disease Score with empirically derived weights. *Med Care*. 1995;33:783-795.
10. Kreiger N, Chen JT, Waterman PD, Soobader MJ, Subramanian SV, Carson R. Geocoding and monitoring US socioeconomic inequalities in mortality and cancer incidence: does choice of area-based measure and geographic level matter? The Public Health Disparities Geocoding Project. *Am J Epidemiol*. 2002;156:471-482.
11. Liang K, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika*. 1986;73:13-22.
12. Scott SA, Falcao A, Evens RP, Elenbaas JK; DRUGDEX Editorial Staff. DRUGDEX drug evaluations: carbamazepine. In: Klasco RK, ed. *DRUGDEX System*. Greenwood Village, Colo: Thomson Micromedex; 2005.
13. Pitterle ME, Sorkness CA, Wiederholt JB. Use of serum drug concentrations in outpatient clinics. *Am J Hosp Pharm*. 1985;42:1547-1552.
14. Bussey HI, Hoffman EW. A prospective evaluation of therapeutic drug monitoring. *Ther Drug Monit*. 1983;5:245-248.
15. Brodie MJ, Feely J. Practical clinical pharmacology: therapeutic drug monitoring and clinical trials. *BMJ*. 1988;296:1110-1113.
16. McKee PJ, Larkin JG, Brodie AF, Percy-Robb IW, Brodie MJ. Five years of anti-convulsant monitoring on site at the epilepsy clinic. *Ther Drug Monit*. 1993;15: 83-90.