Laboratory Monitoring of Drugs at Initiation of Therapy in Ambulatory Care

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BACKGROUND AND OBJECTIVES: Product labeling and published guidelines reflect the importance of monitoring laboratory parameters for drugs with a risk of organ system toxicity or electrolyte imbalance. Limited information exists about adherence to laboratory monitoring recommendations. The objective of this study was to describe laboratory monitoring among ambulatory patients dispensed medications for which laboratory testing is recommended at therapy initiation.

DESIGN AND SUBJECTS: We conducted a retrospective cross-sectional analysis of patients in 10 geographically distributed health maintenance organizations who were newly prescribed medications with recommended laboratory test monitoring. The main outcome measure was the proportion of initial drug dispensing without recommended baseline laboratory monitoring for 35 newly initiated drugs or drug classes.

RESULTS: One hundred seven thousand, seven hundred sixty-three of 279,354 (39%) initial drug dispensings occurred without recommended laboratory monitoring. Patients without monitoring were younger than patients who had monitoring (median 57 vs 61 years, $P < .001$). Thirty-two percent of dispensings where a serum creatinine was indicated did not have it evaluated (range across drugs, 12% to 61%); 39% did not have liver function testing (range 10% to 75%); 32% did not have hematologic monitoring (range 9% to 51%); and 34% did not have electrolyte monitoring (range 20% to 62%) ($P < .001$).

CONCLUSIONS: Substantial opportunity exists to improve laboratory monitoring of drugs for which such monitoring is recommended. This study emphasizes the need for research to identify the clinical implications of not conducting recommended laboratory monitoring, existing barriers to monitoring, and methods to improve practice.

KEY WORDS: laboratory monitoring; ambulatory; drug therapy.

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Errors of medication use are common and occur throughout the drug use continuum.^{1,2} Most attention to medication use errors has been in hospitalized patients. However, medication use errors in the ambulatory care environment can be errors of omission, commission, or prevention and carry risks amplified in importance by the numbers of patients receiving treatment.^{1,3-18}

One subset of medication use errors is related to laboratory monitoring for drugs that carry a risk of organ system toxicity or that require dosage adjustment in the presence of organ dysfunction. Laboratory monitoring errors occur when there is failure to conduct indicated laboratory tests, when there is avoidable delay in responding to abnormal tests, or when there is inadequate follow-up.^{17,18} The importance of laboratory monitoring for drugs such as divalproex, isotretinoin, ketoconazole, lithium, metformin, rifampin, carbamazepine, and allopurinol is reflected in product labeling and published guidelines.¹⁹⁻²¹ The few published studies evaluating adherence to laboratory monitoring recommendations document that monitoring recommendations are not followed for 27% to 91% of patients.²¹⁻²⁹

Better understanding of patterns of laboratory monitoring associated with drug therapy will inform patient safety interventions and potentially affect therapy costs and decrease complications. We undertook the current study to assess laboratory monitoring for organ injury, organ dysfunction, and electrolyte abnormalities requiring correction among patients initiating medications for which product labeling or other guideline recommends monitoring. The specific aims of this study were to (1) identify gaps in recommended laboratory monitoring at initiation of therapy; (2) describe variations in baseline laboratory monitoring by age, sex, number of chronic diseases, drug, and health plan; and (3) assess the utility of automated data in identifying lack of laboratory monitoring. The primary outcome was the proportion of initial drug dispensings without baseline laboratory monitoring as determined by automated data.

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METHODS

Study Setting

The HMO Research Network (HMORN) Center for Education and Research in Therapeutics (CERTs) is a network of 10 HMOs that collaborate on pharmacoepidemiology, pharmacoeconomics, and outcomes education and research in therapeutics.^{30,31} The organizations that comprise the HMORN CERTs represent staff, group, network, and independent practice association models that provided health care for approximately 7,000,000 people in over 1,000 locations across the United States in the year 2000. The HMORN CERTs health plans serve diverse populations. All serve Medicaid and Medicare beneficiaries, as well as commercially insured members. The Institutional Review Boards of each participating HMO approved this study.

Study Design and Population

This was a cross-sectional study conducted in new users of medications designated as drugs for which laboratory monitoring is recommended upon therapy initiation. The study sample was drawn from a data set that included 200,000 representative health plan members from each of the 10 participating HMOs (i.e., 2,000,000 individuals). Sampling scheme and demographic distribution of this population have been described elsewhere.³¹

The subset of patients in the 2 million person data set who met the following criteria was included in the current study: health plan members with a pharmacy benefit for at least 180 days before and 14 days after the index dispensing of a drug between July 1, 1999 and June 16, 2001. An index dispensing was defined as no dispensing of the same drug for at least the previous 180 days.

Determination of Drugs and Laboratory Monitoring

Drugs and laboratory tests studied were determined using a sequential process. First, drugs were identified that had Black Box Warnings (BBWs) for initial laboratory monitoring. Black Box Warnings are typically used for drugs with life threatening adverse event risks. A comprehensive list of BBWs through December 2000 was compiled by reviewing the entire Physicians Desk Reference 2000 and supplementing that information with the most current information from the FDA website.^{32,33} Medications excluded from study were those used primarily in the inpatient setting (e.g., trovafloxacin) or not dispensed via prescription through a pharmacy (e.g., administered in a physician's office). Nationally available published guidelines and internal clinical guidelines from participating organizations were searched for other laboratory monitoring recommendations related to medications (e.g., American College of Cardiology/American Heart Association Guidelines; Kaiser Permanente National Evidence-Based Guidelines).³⁴⁻³⁸ A draft list of recommended drug-laboratory monitoring pairs was compiled from these sources. This list was circulated to practicing physicians, clinical pharmacists, and clinician-leaders in the HMOs and to members of the CERTs national advisory committee. Their feedback was incorporated into the preliminary list of drugs requiring laboratory monitoring. The list therefore reflected not only drugs with

laboratory testing recommended in product labeling, but also reflected the consensus of the clinicians at the 10 participating HMOs.

The frequency of dispensings across all 10 organizations for drugs in the preliminary list was determined. Drugs with fewer than 100 dispensings were excluded. Excluded drugs were auranofin, aurothioglucose, chloramphenicol, cidofovir, clofibrate, dantrolene, disopyramide, felbamate, flucytosine, foscarnate, fosphenytoin, gold sodium thiomalate, oxandrolone, oxymetholone, penicillamine, tocainide, and tolcapone. The final list of included drugs is in Table 1.

Because recommendations for the timeframe of baseline laboratory monitoring were not consistent, we chose the laboratory monitoring time period for this study based on consensus of clinicians and researchers at the participating sites. It was agreed that clinicians might rely on laboratory test results for up to 6 months before initiating a drug or might order a test to be conducted within 2 weeks after initiating a drug for clinically stable patients. A laboratory monitoring error was therefore defined as failure to perform indicated laboratory monitoring during the 180 days before or 14 days after drug dispensing. Laboratory tests were determined using each site's laboratory test codes.

Six drugs requiring monitoring were selected for medical record review to assess accuracy of the administrative data. The laboratory tests these drugs represented included serum creatinine for metformin and digoxin, aspartate or alanine aminotransferase (AST or ALT) for isotretinoin, carbamazepine, and statins, and thyroid function for amiodarone. For each drug-laboratory monitoring type, medical records of 10 patients from each of the 10 sites (100 patients total for each drug; 600 total medical records [chosen by patient, not by practice]) without laboratory monitoring documented in administrative data were randomly selected to determine whether the monitoring was also not completed according to the medical record. For each patient, the record reviewed was the record maintained by the prescribing provider. To identify laboratory testing, the abstractor reviewed both the laboratory test results and the progress notes sections of the medical record for each patient. The absence of laboratory testing based on administrative data was confirmed as an error only if the abstractor found no mention in either of these medical record sections that the test had been performed. The only situation where a selected medical record was not reviewed was when the abstractor was unable to obtain the medical record from the patient's prescribing provider for the study time period.

Statistical Analysis

The unit of analysis was initial drug dispensings between July 1, 1999 and June 16, 2001. We defined the date a laboratory test was performed as the posting date in the administrative database. For each drug/drug class, the proportion that received all appropriate test(s) was calculated. For selected drugs/drug classes, the proportion receiving specific tests was also evaluated. Univariate statistics were computed to describe the characteristics of persons receiving initial drug dispensings. The presence of specific chronic diseases was determined using the chronic disease score (CDS) method of Clark et al.³⁹ For selected drugs, the Pearson χ^2 test was

Table 1. Estimated Laboratory Monitoring of Selected Drugs at Initiation of Therapy

Drug	Laboratory Blood Test(s) to Monitor*	Number of Dispensings (range across HMOs)	Percent of Dispensings without Monitoring of all Recommended Laboratory Tests (range across HMOs)
Allopurinol	SCR	4,422 (235 to 514)	34.5 (23.2 to 49.0)
Amiodarone	TSH or T4 or T3, ALT or AST	1,551 (37 to 238)	57.2 (45.3 to 80.2)
Angiotensin-converting enzyme inhibitors†	SCR, K+	48,682 (3,011 to 7,914)	39.2 (26.0 to 45.6)
Angiotensin receptor blockers‡	SCR, K+	8,731 (322 to 1,504)	34.1 (21.5 to 42.6)
Azathioprine	CBC, ALT or AST	679 (23 to 113)	24.5 (17.3 to 34.8)
Carbamazepine	CBC, ALT or AST	2,966 (156 to 551)	53.6 (43.9 to 61.9)
Cyclosporine	SCR	336 (14 to 50)	18.8 (8.6 to 27.8)
Digoxin	SCR, K+	6,277 (186 to 938)	27.4 (18.6 to 43.0)
Divalproex (valproate sodium, valproic acid)	ALT or AST, CBC	4,423 (279 to 562)	51.8 (41.8 to 60.2)
Diuretics§	SCR, K+	78,903 (5,075 to 11,381)	39.5 (29.3 to 47.2)
Fibrates	ALT or AST	5,382 (273 to 812)	33.2 (24.8 to 44.7)
Flutamide	ALT or AST	120 (2 to 31)	53.3 (14.3 to 100)
Ganciclovir	SCR, CBC, ANC, ELE, MG+, CA+	142 (5 to 32)	59.2 (12.5 to 100)
Interferon α 2b	CBC, TSH or T4 or T3, ALT or AST	190 (8 to 33)	52.1 (36.7 to 87.5)
Interferon α 2b+Ribavirin	CBC, HGB, TSH or T4 or T3, ALT or AST, PRG	536 (33 to 84)	43.3 (26.8 to 64.7)
Isoniazid	ALT or AST	1,114 (9 to 282)	38.6 (22.2 to 51.5)
Ketoconazole (oral)	ALT or AST, BILI, AKP	2,864 (79 to 567)	85.0 (72.2 to 91.0)
Lithium	TSH or T4 or T3, SCR, CBC, NA+ and K+	1,547 (60 to 239)	69.2 (46.7 to 84.1)
Metformin	SCR	13,341 (823 to 2,131)	25.8 (15.2 to 35.9)
Methotrexate	ALT or AST, SCR, CBC	1,681 (94 to 238)	25.5 (8.9 to 39.9)
Methyldopa	ALT or AST, CBC	516 (24 to 95)	66.1 (42.3 to 86.2)
Nefazodone	ALT or AST	4,147 (185 to 737)	67.2 (59.4 to 76.5)
Niacin	ALT or AST	1,465 (21 to 296)	37.1 (14.0 to 55.4)
Pemoline	ALT	70 (1 to 12)	57.1 (0 to 88.9)
Phenytoin	ALT or AST	2,262 (117 to 303)	49.8 (40.5 to 65.3)
Potassium supplements	K+, SCR	19,176 (1,195 to 2,924)	24.4 (15.1 to 32.6)
Primidone	CBC, ALT or AST	414 (15 to 64)	55.1 (47.8 to 66.0)
Procainamide	CBC	169 (1 to 47)	21.9 (0 to 34.0)
Quinidine	K+, ALT or AST, SCR	72 (2 to 21)	76.4 (0 to 100)
Retinoids (oral)*	ALT or AST, TRG, PRG	2,926 (153 to 448)	41.6 (7.2 to 89.3)
Rifampin	ALT or AST	925 (31 to 151)	66.7 (47.6 to 83.8)
Statins#	ALT or AST	55,068 (3,310 to 7,748)	37.3 (30.2 to 54.3)
Terbinafine	ALT or AST, SCR	4,449 (14 to 1,337)	68.2 (56.4 to 82.7)
Ticlopidine	CBC, ALT or AST	161 (6 to 34)	48.5 (22.2 to 75.0)
Thiazolidinediones**	ALT or AST	3,647 (28 to 803)	23.8 (2.9 to 75.0)
Total (all drugs)		279,354 (18,608 to 39,933)	38.6 (29.3 to 46.3)

*AKP, alkaline phosphatase; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; BILI, bilirubin; BUN, blood urea nitrogen; CA+, calcium; CBC, complete blood count; SCR, creatinine (serum); ELE, electrolytes (sodium, potassium, chloride, bicarbonate); FLP, fasting lipid profile; GGT, gamma-glutamyl transferase (GGTP); HGB, hemoglobin; LDH, lactate dehydrogenase; MG+, magnesium; NA+, sodium; K+, potassium; PRG, Pregnancy (serum or urine); T3, triiodothyronine; T4, thyroxine; T34, triiodothyronine or thyroxine; TRG, triglycerides; TSH, thyroid stimulating hormone; WBC, white blood cell count.

†Angiotensin-converting enzyme inhibitors (ACEI) include benazepril, captopril, enalapril, fosinopril, lisinopril, monopril, quinapril, and ramipril, and combinations of ACEI with hydrochlorothiazide.

‡Angiotensin receptor blockers (ARB) include candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan, and combinations of ARB with hydrochlorothiazide.

§Diuretics include bumetanide, furosemide, hydrochlorothiazide, spironolactone, triameterene, spironolactone+hydrochlorothiazide, triameterene+hydrochlorothiazide, and other thiazide-type diuretics.

||Fibrates include gemfibrozil and fenofibrate.

*Retinoids includes isotretinoin and acetrelin.

#Statins include atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin.

**Thiazolidinediones include pioglitazone and rosiglitazone.

used to test whether an association existed between those receiving the laboratory test(s) compared with those not receiving the laboratory test(s) by age group, gender, CDS group, and health plan. To test differences in the continuous, non-normally distributed age and CDS variables, the Wilcoxon signed rank test was used. The proportion of errors confirmed by record review was calculated overall, by drug, and by laboratory test type.

The timing of laboratory testing relative to drug dispensing was considered a continuous variable categorized into 4 time periods that spanned 180 days before dispensing to 14 days after dispensing. Laboratory tests occurring before drug dispensing were of interest because tests completed well in advance of the first dispensing could reflect a chance association of laboratory monitoring with drug dispensing rather than intentional monitoring.

FIGURE 1. Proportion of Drug Dispensings without All Recommended Laboratory Monitoring at Each HMO.

RESULTS

The proportion of drug dispensings without all recommended laboratory monitoring at each of the participating HMOs is shown in Figure 1. Drug dispensing-laboratory test pairs evaluated are shown in Tables 1–3. These drugs had 279,354 index dispensings across the 10 HMOs 149,731 (54%) to females and 129,623 (46%) to males. Over 90% of all index drug dispensings were to patients in either a traditional HMO insurance plan type ($n=184,921$; 66%) or a Medicare plan type ($n=71,754$; 26%). Of initial dispensings, 107,763 (39%) occurred without some or all recommended laboratory monitoring. Across the HMOs, the percentage of dispensings without recommended monitoring varied from 29% to 46%. Patients without laboratory monitoring were younger (median 57 vs 61 years of age; $P<.001$; Fig. 2) and had a lower CDS (median 3 vs 4; $P<.001$; Fig. 3).

When monitoring was evaluated by drug by organ system, no record of serum creatinine measurement was found in 32% of dispensings (range across drugs 12% to 61%); no liver function testing was found in 39% (range 10% to 75%); no hematologic monitoring was found in 32% (range 9% to 51%); and no electrolytes/minerals monitoring was found in 34% (range 20% to 62%) ($P<.001$). For example, in 35% of initial dispensings of allopurinol, no serum creatinine was found, and 50% of patients initiated on phenytoin did not have an ALT or AST measured.

Laboratory monitoring percentages overall and by selected drug laboratory test pairs are in Tables 1–3. For example, for an angiotensin-converting enzyme inhibitor (ACEI), in 39% of dispensings, both serum creatinine and serum potassium were not monitored; however, when the individual tests were evaluated, a creatinine was not measured in 32% of ACEI dispensings, and a potassium was not evaluated in 37%.

Thyroid function was evaluated less frequently than other laboratory tests (data not shown in tables). Specifically, 47% of patients started on amiodarone, 50% of patients initiated on interferon α , 26% of patients started on interferon α +ribavirin, and 45% of patients started on lithium did not have thyroid function evaluated.

Evaluation of the timing of completion of laboratory monitoring revealed that 59.7% of monitoring occurred within the 28-day period that comprised 14 days before to 14 days after drug dispensing. Only 9.6% of monitoring occurred in the 15th to 29th days before drug dispensing, and 30.7% of monitoring occurred in the 30th to 180th days before dispensing.

The absence of laboratory testing in administrative records was confirmed as correct for 78% for metformin-creati-

Table 2. Percent of Drug Dispensings without Recommended Alanine Aminotransferase or Aspartate Aminotransferase Monitoring

Drug	ALT or AST* (95% Confidence Interval)
Amiodarone	36.2 (33.8, 38.7)
Azathioprine	22.7 (19.6, 26.0)
Carbamazepine	49.3 (47.5, 51.1)
Divalproex (valproate sodium, valproic acid)	47.0 (45.5, 48.4)
Fibrates†	33.2 (31.9, 34.5)
Flutamide	53.3 (44.0, 62.5)
Interferon α 2b	9.5 (5.7, 14.6)
Interferon α 2b+Ribavirin	7.8 (5.7, 10.4)
Isoniazid	38.6 (35.7, 41.5)
Ketoconazole (oral)	74.9 (73.2, 76.4)
Methotrexate	16.8 (15.1, 18.7)
Methyldopa	58.7 (54.3, 63.0)
Nefazodone	67.2 (65.8, 68.6)
Niacin	37.1 (34.7, 39.7)
Pemoline	57.1 (44.7, 68.9)
Phenytoin	49.8 (47.7, 51.9)
Primidone	58.0 (53.1, 62.8)
Quinidine	72.2 (60.4, 82.1)
Retinoids (oral)‡	27.2 (25.6, 28.9)
Rifampin	66.7 (63.6, 69.7)
Statins§	37.3 (36.9, 37.7)
Terbinafine	42.5 (41.1, 44.0)
Ticlopidine	42.2 (34.5, 50.3)
Thiazolidinediones	23.7 (22.4, 25.2)

*ALT, alanine aminotransferase; AST, aspartate aminotransferase.

†Fibrates include gemfibrozil and fenofibrate.

‡Retinoids includes isotretinoin and acetrelin.

§Statins include atorvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin.

||Thiazolidinediones include pioglitazone and rosiglitazone.

nine, 72% for digoxin-creatinine, 81% for isotretinoin-ALT or AST, 84% for statins-ALT or AST, 89% for carbamazepine-ALT or AST, and 76% for amiodarone-thyroid function. By type of test, administrative claims confirmed as failures to receive

Table 3. Percent of Drug Dispensings without Recommended Serum Creatinine Monitoring

Drug	Serum Creatinine (95% Confidence Interval)
Allopurinol	34.5 (33.1, 35.9)
Angiotensin-converting enzyme inhibitors*	32.3 (31.9, 32.7)
Angiotensin receptor blockers†	29.6 (28.7, 30.6)
Cyclosporine	18.8 (14.7, 23.3)
Digoxin	24.5 (23.4, 25.6)
Diuretics‡	34.4 (34.0, 34.7)
Ganciclovir	12.0 (7.1, 18.5)
Lithium	42.0 (39.5, 44.6)
Metformin	25.8 (25.1, 26.6)
Methotrexate	17.5 (15.8, 19.5)
Potassium supplements	21.4 (20.8, 21.9)
Quinidine	48.6 (36.6, 60.7)
Terbinafine	60.9 (59.5, 62.4)

*Angiotensin-converting enzyme inhibitors (ACEI) include benazepril, captopril, enalapril, fosinopril, lisinopril, monopril, quinapril, and ramipril, and combinations of ACEI with hydrochlorothiazide.

†Angiotensin receptor blockers (ARB) include candesartan, eprosartan, irbesartan, losartan, telmisartan, valsartan, and combinations of ARB with hydrochlorothiazide.

‡Diuretics include bumetanide, furosemide, hydrochlorothiazide, spironolactone, triamterene, spironolactone+hydrochlorothiazide, triamterene+hydrochlorothiazide, and other thiazide-type diuretics.

FIGURE 2. Laboratory Monitoring in Relation to Age.

monitoring by record review were 75% for serum creatinine, 76% for thyroid function, and 84% for ALT or AST.

Two factors occurred in situations where there was a discrepancy between administrative data and medical records. A laboratory test documented in the medical record but not in administrative data accounted for 11 of 29 (38%) nonconcordant records for digoxin, 7 of 16 (44%) for statins, 11 of 11 (100%) for carbamazepine, 20 of 21 (95%) for metformin, 17 of 25 (68%) for amiodarone, and 17 of 18 (94%) for isotretinoin. The second factor was that the first drug dispensing occurred during a hospitalization, resulting in the record in the ambulatory setting not being the true index dispensing. This occurred for digoxin 12 of 29 (41%) and amiodarone 8 of 25 (32%). Nonindex dispensing of a statin was observed at one HMO and occurred because of a formulary switch program. In this situation, a different statin had been previously dispensed to patients in 9 of 16 (56%) nonconcordant records, so although the dispensing in administrative data was the initial dispensing of the *identified* statin, it was not the initial dispensing of *any* statin.

DISCUSSION

Although all drugs evaluated in this study had laboratory testing recommended in BBW or clinical guidelines, we observed wide variations in testing rates. For example, 74% of patients initiated on methotrexate had a serum creatinine, a complete blood count, and an ALT or AST monitored. In comparison, a

complete blood count and an ALT or AST were monitored in 46% of patients starting carbamazepine; only 15% of patients starting ketoconazole had a bilirubin, an alkaline phosphatase, and an ALT or AST test completed. Many factors could contribute to these variations. Prescribers may be more likely to monitor when a drug is prescribed for prolonged treatment. Prescribers could be more likely to monitor if they had previously cared for patients who experienced drug toxicity. Additionally, for drugs such as diuretics and statins, there is little evidence to support the need for baseline monitoring and it might be reasonable to forego baseline testing for a low risk patient.

We found that ALT or AST was evaluated in 76% of patients started on the thiazolidinediones rosiglitazone or pioglitazone. This is in contrast to the findings of Graham et al.²³ regarding troglitazone, a thiazolidinedione removed from the United States market in March 2000 after cases of acute liver failure were reported with its use.⁴⁰ Graham and colleagues evaluated the FDA risk management efforts (i.e., labeling changes and "Dear Healthcare Professional" letters) related to liver enzyme monitoring in patients taking troglitazone. After 4 separate FDA interventions, only 44.6% of patients had baseline testing.²³ The timeframe for evaluating thiazolidinedione monitoring in our study spans the timeframe of the FDA risk management efforts and goes beyond into the first 6 months of 2001. Our monitoring proportions are higher than those observed by Graham, potentially because of heightened awareness of the toxicity risk surrounding removal of troglitazone from the market.

Our study indicates the utility of merging pharmacy and laboratory claims data in ambulatory practice. We believe that assessment of claims data can be useful because it is relatively straightforward to implement and because record reviews in 10 health plans indicate that claims data are relatively accurate in most situations. The logical use of claims data is to assess overall, rather than individual performance. Because our work was conducted in a heterogeneous set of organizations and information systems, these results are likely generalizable to other ambulatory health care settings in the United States.

As demonstrated in our results, using claims data to assess quality in ambulatory practice involves a "trade-off" between the accessibility of claims data and its completeness. A limitation to the use of claims data is the inability to identify drug dispensing or laboratory testing performed in hospitals, because this information is typically not reported in claims data. To improve the accuracy of claims-based analysis in future work, we recommend, if feasible, excluding patients who have been hospitalized if hospital laboratory monitoring information is not available for specific tests in claims data. Our results also indicate that a monitoring system should focus on drug classes rather than individual drugs. This avoids misclassification of monitoring in patients switched from one drug to another within a drug class such as we observed with statins.

We could not identify tests ordered but not performed. It was not possible to separate physician noncompliance from patient nonadherence. We were also unable to determine subtle indicators of physician behavior, such as whether laboratory testing was for the specific purpose of baseline drug monitoring or whether the ordering clinician reviewed or acted on test results. Differences we observed in monitoring by

FIGURE 3. Laboratory Monitoring in Relation to Chronic Disease Score.

age, sex, and chronic diseases could reflect differences in the frequencies with which laboratory tests were ordered for reasons other than intentional drug safety monitoring.

We were not able to control for the effect of certain physician, clinic, and patient factors. We evaluated variation by HMO, but we could not evaluate variation by physician or clinic, because we did not have that information. However, we believe these potential limitations do not detract from the importance of the study results.

Our work documents that opportunities exist for improving laboratory monitoring at initiation of therapy. These findings do not imply, however, that physicians are not attentive to test results nor that they are uninterested in improvement. Poon et al.⁴¹ found that only 41% (of 262) of internal medicine physicians were satisfied with how they managed laboratory test results, despite the fact that they spent more than 70 minutes per work day doing so. Among other features, these physicians wanted a system that assisted in tracking test orders to completion. Many systems have been suggested as tools to improve laboratory monitoring such as results management systems imbedded in patients' electronic medical records,⁴¹ electronic tools that focus on abnormal test results,⁴¹ and systems that use electronic linkages between laboratory and pharmacy data to automatically warn about missing laboratory tests.⁴² These and other systems make use of technology that can reduce errors and patient harm and enable both individual and organizational quality improvement.⁴³⁻⁴⁵

CONCLUSIONS

We conclude that a substantial proportion of individuals who began taking drugs that carry a risk of organ system toxicity, cause electrolyte abnormalities, or require dosage modification in organ dysfunction do not receive recommended baseline laboratory monitoring. Our study substantiates the utility of merging pharmacy and laboratory data that can then be used to enable quality of care improvement efforts. It provides information to assist in designing clinical outcomes and cost effectiveness evaluations relative to recommended laboratory monitoring. We believe this study can provide the motivation to assess implications of failing to monitor as recommended. We also believe this study can provide the impetus to both implement routine monitoring systems and develop methods to improve compliance, or based on results of clinical outcomes evaluations, if monitoring does not improve outcomes, to revise monitoring recommendations.

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REFERENCES

- Bates DW, Boyle DL, Vander Vliet MB, et al. Relationship between medication errors and adverse drug events. *J Gen Intern Med.* 1995;10:199-205.
- Kohn LT, Corrigan JM, Donaldson MS, eds. *To Err is Human: Building a Safer Health System.* Washington, DC: Committee on Quality of Health Care in American, Institute of Medicine. National Academy Press; 1999.
- Lazarou J, Pomeranz BH, Corey PH. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA.* 1998;279:1200-5.
- Bates DW, Cullen DJ, Laird N, et al. Incidence of adverse drug events and potential adverse drug events. *JAMA.* 1995;274:29-34.
- Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *JAMA.* 1998;280:1311-6.
- Classen DC, Pestotnik SL, Evans RS, et al. Adverse drug events in hospitalized patients. *JAMA.* 1997;277:301-6.
- Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Engl J Med.* 1991;324:377-84.
- Leape LL, Bates DW, Cullen DJ, et al. Systems analysis of adverse drug events. *JAMA.* 1995;274:35-43.
- Schneeweiss S, Hasford J, Gottler M, et al. Admissions caused by adverse drug events to internal medicine and emergency departments in hospitals: a longitudinal population-based study. *Eur J Clin Pharmacol.* 2002;58:285-91.
- Gandhi TK, Burstin HR, Cook EF, et al. Drug complications in outpatients. *J Gen Intern Med.* 2000;15:149-54.
- Hanlon JT, Schmader KE, Koronkowski MJ, et al. Adverse drug events in high risk older outpatients. *J Am Geriatr Soc.* 1997;45:945-8.
- Hutchinson TA, Flegal KM, Kramer MS, et al. Frequency, severity and risk factors for adverse drug reactions in adult out-patients: a prospective study. *J Chronic Dis.* 1986;39:533-42.
- Gandhi TK, Weingart SN, Borus J, et al. Patient safety adverse drug events in ambulatory care. *N Engl J Med.* 2003;348:1556-64.
- Gurwitz JH, Field TS, Harrold LR, et al. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. *JAMA.* 2003;289:1107-16.
- Steiner JF, Robbins LJ, Hammermeister KE, et al. Incidence of digoxin toxicity in outpatients. *West J Med.* 1994;161:474-8.
- Johnson JA, Bootman JL. Drug-related morbidity and mortality. A cost-of-illness model. *Arch Intern Med.* 1995;155:1949-56.
- Kennedy AG, MacLean CD. Clinical inertia: errors of omission in drug therapy. *Am J Health-Syst Pharm.* 2004;61:401-4.
- Leape LL, Lawthers AG, Brennan TA, Johnson WG. Preventing medical injury. *Qual Rev Bull.* 1993;19:144-9.
- Beach JE, Faich G, Bormel G, Sasnowski FJ. Black Box Warnings in prescription drug labeling: results of a survey of 206 drugs. *Food Drug Law J.* 1998;53:403-11.
- Hande RK, Noone RM, Stome WJ. Severe allopurinol toxicity. Description and guidelines for prevention in patients with renal insufficiency. *Am J Med.* 1984;76:47-56.
- Schoenenberger RA, Tanasijevic MJ, Jha A, Bates DW. Appropriateness of antiepileptic drug level monitoring. *JAMA.* 1995;274:1622-6.
- Roblin DW, Nielsen DM. Assessment of quality in adult primary care: developing process measures from administrative data. *Clin Perform Qual Health Care.* 1994;2:200-8.
- Graham DJ, Drinkard DR, Shatin D. Study of liver enzyme monitoring in patients receiving troglitazone. *Pharmacoepidemiol Drug Saf.* 2000;(suppl 1):S131.
- Emslie-Smith AM, Boyle DI, Evans JM, et al. Contraindications to metformin therapy in patients with type 2 diabetes: a population-based study of adherence to prescribing guidelines. *Diabet Med.* 2001;18:483-8.
- Abokire SA, Karson AS, Fiskio J, Bates DW. Use and monitoring of "statin" lipid-lowering drugs compared with guidelines. *Arch Intern Med.* 2001;161:53-8.
- Tegeder I, Levy M, Muth-Selbach U, et al. Retrospective analysis of the frequency and recognition of adverse drug reactions by means of automatically recorded laboratory signals. *Br J Clin Pharmacol.* 1999;47:557-64.

27. **Selby JV, Ettinger B, Swain BE.** First 20 months experience with use of metformin for type 2 diabetes in a large HMO. *Diabetes Care.* 1999;22:38–44.
28. **Calabrese AT, Coley KC, DaPos SV, et al.** Risk of lactic acidosis with metformin therapy. *Arch Intern Med.* 2002;162:434–7.
29. **Graham DJ, Drinkard DR, Shatin D, et al.** Liver enzyme monitoring in patients receiving troglitazone. *JAMA.* 2001;286:831–3.
30. **Chan KA, Davis RL, Gunter MJ, et al.** The HMO Research Network. In: Strom BL, ed. *Pharmacoepidemiology.* 4th ed. Chichester, UK: Wiley; 2005 (in press).
31. **Simon SR, Chan KA, Soumerai SB, et al.** Potentially inappropriate medication use among elderly persons in the United States HMOs, 2000–2001. *J Am Geriatr Soc.* 2005;53:227–32.
32. **Physician's Desk Reference.** 54th ed. Montvale, NJ: Medical Economics Company Inc.; 2000.
33. **Food and Drug Administration.** <http://www.fda.gov/medwatch/safety/2000/safety00.htm>.
34. **Baker DW, Chin MH, Cinquegrani MP, et al.** ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. *J Am Coll Cardiol.* 2001;38:2101–13.
35. **Generali JA.** Black box drug warnings: analgesics, anticonvulsants and anti-infectives. *Hosp Pharm.* 2002;37:1006–23.
36. **Generali JA.** Black box drug warnings: antineoplastics, vitamins and miscellaneous agents. *Hosp Pharm.* 2002;37:1228–46.
37. McEvoy GK, ed. *AHFS Drug Information* 1999. Bethesda, MD: American Society of Health-System Pharmacists; 1999.
38. **Micromedex[®] Healthcare Series.** Thomson Micromedex. Greenwood Village, Colo (Edition expires 06/2002).
39. **Clark DO, Von Korff M, Saunders K, et al.** A chronic disease score with empirically derived weights. *Med Care.* 1995;33:783–95.
40. **Henney JE.** Withdrawal of troglitazone and cisapride. *JAMA.* 2000;283:2228.
41. **Poon EG, Gandhi TK, Sequist TD, et al.** I wish I had seen this test result earlier: dissatisfaction with test result management systems in primary care. *Arch Intern Med.* 2004;164:2223–8.
42. **Schiff GD, Klass D, Peterson J, Shah G, Bates DW.** Linking laboratory and pharmacy: opportunities for reducing errors and improving care. *Arch Intern Med.* 2003;163:893–900.
43. **Shabot MM, LoBue M, Chen J.** Wireless clinical alerts for physiologic, laboratory and medication data. *Proc AMIA Symp* 2000: 789–93.
44. **Rind DM, Safran C, Phillips RS, et al.** Effect of computer-based alerts on the treatment and outcomes of hospitalized patients. *Arch Intern Med.* 1994;154:1511–7.
45. **Raschke RA, Goldhare B, Wunderlich TA, et al.** A computer alert system to prevent injury from adverse drug events: development and evaluation in a community teaching hospital. *JAMA.* 1998; 280: 1317–20.

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