BRIEF REPORT: Laboratory Safety Monitoring of Chronic Medications in Ambulatory Care Settings

Judith S. Hurley, MS, RD,[1] Melissa Roberts, MS,[1] Leif I. Solberg, MD,[2] Margaret J. Gunter, PhD,[3] Winnie W. Nelson, PharmD, MS,[2] Linda Young, PharmD,[4] Floyd J. Frost, PhD[1]

[1]Center for Pharmacoeconomic and Outcomes Research, Lovelace Respiratory Research Institute, Albuquerque, NM, USA; [2]HealthPartners Research Foundation, Minneapolis, MN, USA; [3]Lovelace Clinic Foundation, Albuquerque, NM, USA; [4]Lovelace Sandia Health Systems, Albuquerque, NM, USA.

OBJECTIVE: To evaluate laboratory safety monitoring in patients taking selected chronic prescription drugs.

DESIGN: Retrospective study using 1999–2001 claims data to calculate rates of missed laboratory tests (potential laboratory monitoring errors). Eleven drugs/drug groups and 64 laboratory tests were evaluated.

SETTING: Two staff/network model health maintenance organizations.

PATIENTS: Continuously enrolled health plan members age $\geq$ 19 years taking $\geq$ 1 chronic medications.

MEASUREMENTS AND MAIN RESULTS: Among patients taking chronic medications (N=29,823 in 1999, N=32,423 in 2000, and N=36,811 in 2001), 47.1% in 1999, 45.0% in 2000, and 44.0% in 2001 did not receive $\geq$ 1 test recommended for safety monitoring. Taking into account that patients were sometimes missing more than 1 test for a given drug and that patients were frequently taking multiple drugs, the rate of all potential laboratory monitoring errors was 849/1,000 patients/year in 1999, 810/1,000 patients/year in 2000, and 797/1,000 patients/year in 2001. Rates of potential laboratory monitoring errors varied considerably across individual drugs and laboratory tests.

CONCLUSIONS: Lapses in laboratory monitoring of patients taking selected chronic medications were common. Further research is needed to determine whether, and to what extent, this failure to monitor patients is associated with adverse clinical outcomes.

KEY WORDS: patient safety; laboratory testing; chronic medications; medical errors; medication safety.
DOI: 10.1111/j.1525-1497.2005.40182.x
J GEN INTERN MED 2005; 20:331–333.

Prior research indicates adverse drug events (ADEs) are a concern in the ambulatory care setting. In one study, 25% of primary care patients reported an adverse drug event.[1] Gandhi et al. found that 18% of primary care patients taking $\geq$ 1 prescription drug reported a drug complication.[2] At a Veterans Administration medical center, 35% of patients taking $\geq$ 5 prescription drugs reported an ADE.[3] Outpatient ADEs led to over 1 million hospitalizations in 1994, nearly 5% of all admissions.[4]

A portion of ADEs in the outpatient setting are related to suboptimal laboratory monitoring of drug therapy, including inadequate use of laboratory tests to monitor organ function and drug levels. Schiff et al. found potassium was commonly prescribed despite presence of hyperkalemia.[5] Graham et al. reported less than 5% of patients taking troglitazone received all recommended liver function tests (LFTs), despite Food and Drug Association (FDA) risk management efforts.[6] Among Medicare outpatients, all ADEs occurred at a rate of 50.1/1,000 person-years and preventable ADEs at a rate of 1.38/1,000 person-years.[7] Monitoring errors were the cause of 60.8% of preventable events, including inadequate laboratory monitoring or clinician failure to act on laboratory results or clinical findings. In nursing homes, inadequate monitoring of warfarin is a common cause of ADEs.[8]

In a retrospective study using outpatient and pharmacy claims from two health maintenance organizations (HMOs), we determined whether patients taking selected chronic medications received recommended laboratory monitoring.

METHODS

Study Population

We determined rates of missed laboratory tests (potential laboratory monitoring errors) in 1999, 2000, and 2001 in patients receiving chronic medications for which specific laboratory monitoring is recommended. The study population comprised ongoing users of a chronic medication and the study was conducted using claims data from two HMOs. In 2000, the two HMOs had approximately 657,000 and 240,000 members. This analysis was part of a larger study. In this analysis, patients from small medical groups (those serving fewer than 30 health plan members) were excluded because the analysis plan for the larger study required exclusion of smaller medical groups.

For each study year, eligible subjects were those members who were 1) continuously enrolled with pharmacy benefits during the study year and for the 6 months prior, 2) affiliated with an HMO medical group for their primary health care, 3) age $\geq$ 19 years as of January 1, and 4) taking a chronic medication throughout the study year and during the prior 6 months (the 6-month look-back period permitted exclusion of patients new to drug therapy).

Patients were required to have obtained sufficient medication to cover at least 6 months of use during the study year, verified through pharmacy claims data. Sensitivity analysis showed that requiring patients to have obtained medication sufficient to cover 80% of the year (9.6 months) would not have substantively affected error rates, but would have reduced sample size considerably. Patients also were required to have had a supply of medication at the end of the study year. This ensured that no patients were included who had intentionally

Accepted for publication October 18, 2004

Neither the first author nor coauthors have any conflicts of interest to report.Aspects of this study were presented at the HMO Research Network annual conference, May 3–5, 2004, Detroit, MI.

Address correspondence and requests for reprints to Dr. Frost: Lovelace Respiratory Research Institute, 2425 Ridgecrest Drive SE, Albuquerque, NM 87108 (e-mail: ffrost@lrri.org).

Table 1. Rates of Potential Laboratory Monitoring Errors

	1999 (*N*=29,823)	2000 (*N*=32,423)	2001 (*N*=36,811)
Patients missing ≥ 1 laboratory test	47% (14,039)	45% (14,575)	44% (16,193)
Potential laboratory monitoring errors per 1,000 patients	849	810	797

discontinued use of the drug during the year and thus no longer needed laboratory monitoring.

Laboratory Monitoring Errors

We selected for evaluation 11 drugs/drug groups and identified recommended laboratory tests and test intervals from the Physician's Desk Reference (PDR),[9] FDA black box warnings, and HMO practice guidelines developed by physicians and clinical pharmacists. We limited our evaluation to tests used to monitor patient safety rather than drug efficacy. Based on final review of the list by two primary care physicians and two clinical pharmacists, we further limited our evaluation to 64 tests deemed of most clinical importance.

In cases where several drugs within the same class had different recommended test intervals, we applied the longer time interval to all drugs in that class (e.g., recommended liver function testing intervals for 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors [statins] range from every 6 months to every 12 months for ongoing users, so we applied the 12-month guideline to all drugs in this class). We identified laboratory tests in claims data using procedure codes.

For the vast majority of drugs examined, guidelines recommended annual laboratory testing in ongoing users of the medication. In that case, we considered the guideline to have been met if the relevant test was conducted at any time during the study year. An exception to this annual testing regimen was warfarin, for which monthly international normalized ratio (INR) or prothrombin time (PT) tests are recommended. In this case, we considered it an error when a patient had no test in 3 out of 12 months (i.e., the patient was unmonitored 25% of the time).

We refer to the absence of the recommended test as a "*potential* laboratory monitoring error" to acknowledge that these may not be *actual* errors. Not all physicians agree with existing laboratory testing recommendations, recommendations differ from source to source, and not all lapses in recommended monitoring result in adverse events.

RESULTS

In 2001, the 36,811 patients taking any of these chronic medications had a mean age of 57.8 years and took an average of 9.3 different medications. The patient group was 50.9% male. The majority were enrolled in a commercial plan (83.1%), rather than a Medicare risk (9.1%) or Medicaid (7.8%) plan. Patient characteristics were similar in 1999 and 2000.

Table 1 shows overall rates of potential laboratory monitoring errors. Between 44.0% and 47.1% of medication users had at least 1 potential laboratory monitoring error per year. Many patients, however, were missing more than 1 laboratory test for a single medication. Additionally, many patients were taking more than 1 chronic medication, with 1 or more lapses in laboratory monitoring occurring for each medication. Thus, the overall annual rate of potential errors in this population was 849/1,000 patients in 1999, 810/1,000 in 2000, and 797/1,000 in 2001.

Table 2 shows the rates of potential laboratory monitoring errors in patients by drug/drug group and test. Rates of potential laboratory monitoring errors in this population varied considerably across individual drugs and tests.

DISCUSSION

Of patients taking 1 or more chronic medications, 44.0% to 47.1% of patients each year did not receive 1 or more recommended laboratory tests. Some of our findings can be compared to those of prior studies. For example, we found that 22% to 27% of patients taking statins did not receive an annual LFT, slightly more than the 15% reported by Smith et al.[10] Most published studies evaluating monitoring practices, however, have concerned patients new to drug therapy. Graham et al. found that during the first 3 months of therapy, less than 5% of patients taking troglitazone received recommended LFTs.[6] Although troglitazone is no longer on the market, the FDA exerted considerable effort to encourage safety monitoring of the drug during the years of this study. Nevertheless, we found that of patients taking troglitazone on an ongoing basis, 7% to 23% did not receive an LFT during a 12-month period.

Some lapses in monitoring may be more serious than others, such as inadequate monitoring of potassium in patients taking angiotension converting enzyme (ACE) inhibitors and spironolactone.[11,12] For some medications there is debate concerning the benefit and necessity of monitoring for acute and chronic complications.[10,13] Even when physicians believe laboratory monitoring is clinically important, however, they may be hampered by the patient not accessing health care; by lack of time during patient visits; by not having easy access to records of the patient's current drug regimen; and by a lack of tracking tools, such as computerized reminders for the physician or mailed reminders to the patient. Our identification of a high level of discrepancy between recommended monitoring and actual use suggests a need for improved systems for adherence and/or modification of monitoring recommendations based on research evidence.

This study has several limitations. First, we may not have captured all laboratory tests in this patient population. Procedure coding errors or missing claims data could have led to overestimating potential error rates. Second, identifying prescription drug use from computerized claims records provides only an indirect picture of actual patient medication use. Not all of the patients in our denominator calculations may have been actually taking the drug and in need of safety monitoring. Such errors could have led to overestimating the size of the denominator population and therefore the error rate. We attempted to minimize this problem by requiring subjects to have evidence of a prescription refill not just during, but pri-

Table 2. Percentage of Patients Taking a Chronic Medication Who Received No Laboratory Monitoring During 1 Year of Continuous Use, by Drug and Test 1999–2001

Drug	Laboratory Testing Regimen Evaluated	1999 Percentage with No Test (Denominator, *n*)	2000 Percentage with No Test (Denominator, *n*)	2001 Percentage with No Test (Denominator, *n*)
Carbamazepine	CBC w/differential and platelets annually	61 (589)	59 (560)	61 (605)
	LFT annually	42 (589)	40 (560)	43 (605)
	Carbamazepine level annually	36 (589)	35 (560)	48 (605)
Valproate sodium, divalproex sodium, valproic acid	LFT annually	37 (567)	33 (588)	38 (612)
	Valproic acid level annually	28 (567)	30 (588)	34 (612)
	CBC w/differential and platelets annually	64 (567)	60 (588)	59 (612)
Lithium	Thyroid function annually	24 (423)	28 (368)	30 (354)
	Creatinine annually	23 (423)	26 (368)	25 (354)
	Urinalysis annually	69 (423)	72 (368)	67 (354)
	Lithium level annually	18 (423)	22 (368)	29 (354)
	Sodium and potassium annually	72 (423)	71 (368)	65 (354)
Troglitazone, pioglitazone, rosiglitazone	LFT annually	*	7 (75)	23 (363)
Statins	LFT annually	22 (10,776)	22 (12,931)	23 (15,972)
Gemfibrozil	LFT annually	28 (1,027)	27 (1,066)	26 (1,182)
ACE inhibitors	Creatinine annually	38 (12,382)	34 (13,181)	32 (14,843)
	Potassium annually	42 (12,382)	39 (13,181)	38 (14,843)
Digoxin	Creatinine annually	34 (1,329)	32 (1,368)	28 (1,324)
	Digoxin annually	59 (1,329)	61 (1,368)	55 (1,324)
	Potassium annually	35 (1,329)	34 (1,368)	32 (1,324)
Furosemide HCTZ, triamterene/HCTZ, spironolactone, potassium chloride	Potassium annually	35 (7,820)	33 (8,690)	33 (9,981)
	Creatinine annually	40 (7,820)	35 (8,690)	33 (9,981)
Metformin	Creatinine annually	29 (2,112)	26 (2,766)	25 (3,453)
	CBC annually	80 (2,112)	79 (2,766)	78 (3,453)
Warfarin	INR (or PT) in 9 months/ year	40 (1,341)	41 (1,487)	42 (1,599)

*Drug not on market.
ACE, angiotensin converting enzyme; CBC, complete blood count; LFT, liver function test; INR, international normalized ratio; HCTZ, hydrochlorothiazide; PT, prothrombin time.

or to and at the end of the study year. Finally, we did not measure the actual rate of adverse events associated with lapses in safety monitoring. This study assesses only the potential for adverse outcomes related to inadequate monitoring; the actual occurrence of adverse drug-related events that could be prevented by laboratory monitoring would be expected to be considerably less frequent.[1,7]

This study found that a large proportion of patients receiving selected chronic medications did not receive recommended laboratory monitoring in the outpatient setting. Although there may be varying opinions about which tests are needed and when, the data suggest that failure to monitor is widespread across drug categories and may not be easily explained by disagreements concerning monitoring regimens. Further research is needed to determine to what degree these lapses in laboratory monitoring are associated with adverse clinical outcomes, to identify relevant methods to improve monitoring, and to clarify monitoring needs.

Funding for this study was provided by the U.S. Agency for Healthcare Research and Quality, task order 290-00-0015-04.

The authors thank Hans Petersen, Kelly Fillbrandt, Karen Engebretson, and Kristen Pokela for data programming; Sally Beaton and Michael Shainline for collection of medical group data; and the U.S. Agency for Healthcare Research and Quality for financial support.

REFERENCES

1. **Gandhi TK, Weingart SN, Borus J, et al.** Adverse drug events in ambulatory care. N Engl J Med.. 2003;348:1556–64.
2. **Gandhi TK, Burstin HR, Cook EF, et al**. Drug complications in outpatients. J Gen Intern Med. 2000;15:149–54.
3. **Hanlon JT, Schmader KE, Koronkowski MJ, et al.** Adverse drug events in high risk older outpatients. J Am Geriatr Soc. 1997;45:945–8.
4. **Lazarou J, Pomeranz BH, Corey PH.** Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. J Am Med Assoc. 1998;279:1200–5.
5. **Schiff GD, Aggarwal HC, Kumar S, McNutt RA.** Prescribing potassium despite hyperkalemia: medication errors uncovered by linking laboratory and pharmacy information systems. Am J Med. 2000;109:494–7.
6. **Graham DJ, Drinkard CR, Shatin D, Tsong Y, Burgess MJ.** Liver enzyme monitoring in patients treated with troglitazone. J Am Med Assoc. 2001;286:831–3.
7. **Gurwitz JH, Field TS, Harrold LR, et al**. Incidence and preventability of adverse drug events among older persons in the ambulatory setting. J Am Med Assoc. 2003;298:1107–16.
8. **Gurwitz JH, Field TS, Avorn J, Bates DW.** Incidence and preventability of adverse drug events in nursing homes. Am J Med. 2000;109:87–94.
9. Physician's Desk Reference. 54th ed. Oradell, NJ: Medical Economics; 2000.
10. **Smith CC, Bernstein LI, Davis RB, Rind DM, Shmerling RH.** Screening for statin-related toxicity. Arch Intern Med. 200;163:688–92.
11. **Juurlink DN, Mamdani MM, Lee DS, et al.** Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Eng J Med. 2004;351:526–8.
12. **Wrenger E, Muller R, Moesenthin M, et al.** Interaction of spironolactone with ACE inhibitors or angiotensin receptor blockers: analysis of 44 cases. Br Med J. 2003;327:147–9.
13. **Wyllie E, Wyllie R.** Routine laboratory monitoring for serious adverse effects of antiepileptic medications: the controversy. Epilepsia. 1991; 32(suppl 5):S74–S79.