

Prescriber Compliance With Black Box Warnings in Older Adult Patients

Judith A. Ricci, ScD, MS; Charmaine Coulen, MPH; Jan E. Berger, MD, MJ;
Marsha C. Moore, MD, MBA; Angela McQueen, PharmD; and Saira A. Jan, PharmD

The US Food and Drug Administration (FDA) requires that certain prescription medications be accompanied by a black box warning (BBW). A BBW is the strongest warning imposed by the FDA and indicates that clinical or animal toxicity studies have demonstrated that use of the medication is associated with serious risk or hazard that could lead to death or serious injury.¹ A BBW communicates medication-specific risks to the healthcare provider, often emphasizing the need for close monitoring of patients started on these medications and outlining specific clinical management practices to be followed to reduce risk.

Prescriber compliance with BBWs has been shown to be variable and dependent on factors such as the type of warning, patient age, and sex.^{2,3} Types of BBWs include those that require laboratory testing either before therapy initiation, during treatment, or both (ie, drug-laboratory warning); avoiding prescribing in the presence of another specified medication (ie, drug-drug warning); avoiding prescribing in the presence of another specified health condition (ie, drug-disease warning); or knowing the risks associated with prescribing the medication for a specific population. Previous research demonstrated that prescriber BBW compliance tends to be lower for medications with a drug-laboratory warning and for medications prescribed to females and to patients at least 75 years old.^{2,3}

Given limited evidence demonstrating an increased risk of BBW prescribing violations in older adults, the goal of this research was to improve our understanding of the prescribing and patient-monitoring practices of physicians who prescribe medications with a BBW to patients age ≥65 years in an ambulatory care setting.

METHODS © Managed Care & Health Insurance Association, LLC

This research was designed as a retrospective cohort study of the Horizon Blue Cross Blue Shield of New Jersey beneficiary population age ≥65 years. Horizon is a large health plan in the Northeast with approximately 2 million members. Its lines of business include both commercial and Medicare participants. Horizon eligibility and administrative

medical and pharmacy claims records were analyzed to evaluate the management of patients who were prescribed medications with a BBW.

In this article

Take-Away Points / e104

Published as a Web Exclusive

www.ajmc.com

Background: Patients prescribed medications with US Food and Drug Administration–issued black box warnings (BBWs) warrant additional vigilance by prescribers because these drugs can cause serious adverse drug events. Seniors are at greater risk for adverse drug events due to increased medication burden and greater health vulnerability.

Objective: To improve our understanding of the prescribing and patient-monitoring practices of physicians prescribing medications with a BBW to patients age ≥65 years in an ambulatory care setting.

Methods: A retrospective cohort study of administrative pharmacy and medical claims identified 58,190 patients age ≥65 years in the Horizon Blue Cross Blue Shield of New Jersey beneficiary population with ≥1 claim for ≥1 of the 8 targeted medications between January 1, 2005, and December 31, 2005. Medications included carbamazepine, amiodarone, ketoconazole, loop diuretics, methotrexate, cyclosporine, metformin and combinations, and cilostazol. Patients were followed 12 months from the index prescription date to evaluate prescriber compliance with BBWs using operationalized definitions of compliance.

Results: Patients prescribed drugs with a drug-laboratory warning had lower rates of prescriber BBW compliance (0.7%-24.9%) than patients prescribed drugs with a drug-disease warning (84.7%-90.2%).

Conclusions: Administrative claims analysis identified low rates of prescriber compliance with BBWs in managing patients age ≥65 years. Claims analysis may be a cost-effective strategy to monitor prescriber compliance with BBWs in older patients at higher risk.

(*Am J Manag Care.* 2009;15(11):e103-e108)

For author information and disclosures, see end of text.

Take-Away Points

A retrospective cohort study of administrative pharmacy and medical claims was done to evaluate prescriber compliance with black box warnings (BBWs) in patients age ≥ 65 years, using operationalized definitions of compliance.

- Elderly patients prescribed drugs with a drug-laboratory BBW had lower rates of prescriber BBW compliance than patients prescribed drugs with a drug-disease warning.
- Until electronic health records are universally adopted, administrative claims analysis could be a good alternative for monitoring prescriber compliance with BBWs in adults age ≥ 65 years.

tion, including the privacy regulation issued pursuant to the Health Insurance Portability and Accountability Act of 1996.

Defining Black Box Warning Types and Prescriber Compliance

The BBWs for the 8 study medi-

cations were categorized as either drug-disease (ie, metformin and combinations, and cilostazol) or drug-laboratory (ie, carbamazepine, amiodarone, ketoconazole, loop diuretics, methotrexate, and cyclosporine) based on the content of the BBW stipulating either avoidance of prescribing the medication in the presence of another specified health condition or recommendation of laboratory testing in conjunction with treatment (eg, before therapy initiation, during treatment, or both).

Operationalized definitions of BBW prescribing compliance were derived for all 8 study medications. Definitions were derived from the FDA's BBW recommendations and/or recommendations available in the drug insert for managing patients treated with the drugs, and were modified slightly to enable tracking compliance using administrative medical claims records as the basis for evaluation (Table 1). Diagnosis codes defined by the *International Classification of Diseases, Ninth Revision, Clinical Modification* were used to identify specific health conditions in medical claims records. The American Medical Association's *Current Procedural Terminology* codes were used to identify the presence of laboratory tests. Operationalized definitions of BBW-compliant patient management for each medication appear in Table 1.

In describing physician compliance with BBW-specific clinical management practices, the number and percentage of patients who were managed in compliance with the BBW were quantified for each medication by using the operationalized definitions of compliance.

The study period was divided into 3 segments. The index period ranged from January 1, 2005, to December 31, 2005, and was used to identify the first prescription for 1 of the 8 medications with a BBW targeted in this study (ie, the index prescription). The baseline period comprised the 6 months immediately preceding the index prescription date and was used to determine patient prior drug utilization for the medications of interest and prior healthcare utilization. The follow-up period covered the 12 months immediately following the index prescription date and was used to evaluate prescriber compliance with BBWs. Patients were eligible for inclusion in the study if they were at least 65 years old at the beginning of the follow-up period and continuously eligible for pharmacy benefits from July 1, 2004, through December 31, 2006.

Study medications were selected systematically from the universe of Horizon administrative pharmacy claims for patients age ≥ 65 years in 2006. Eight medications or groups of medications were selected based on those with the highest claim volume, clinical relevance to an older population based on the clinical judgment of study authors, and practicability of effectively evaluating prescriber BBW compliance using administrative pharmacy and medical claims records. The 8 medications and groups of medications selected for analysis included carbamazepine, amiodarone, ketoconazole, loop diuretics, methotrexate, cyclosporine, metformin and combinations, and cilostazol (Table 1), which all had a BBW release date prior to the start of the study period.

The study population comprised the 58,190 adults age ≥ 65 years with at least 1 claim for 1 or more of the 8 targeted medications between January 1, 2005, and December 31, 2005. The population was divided into new users and existing users of the target medication for tracking purposes because some of the management recommendations differ for new and existing users of the medications. New users had no claim for a medication of interest within the study baseline period (ie, the 6 months immediately preceding the index prescription date in 2005). Existing users had at least 1 claim for a medication of interest within the baseline period. This research was conducted in compliance with applicable laws governing the use and disclosure of protected health informa-

RESULTS

Rates of BBW-compliant patient management were examined using our operationalized definitions (Table 1). We observed very low rates of physician compliance with the BBW for some medications (Table 2). The lowest rates were observed in patients prescribed drugs with a drug-laboratory warning. Rates ranged from 0.7% (cyclosporine) to 24.9% (loop diuretics). Rates of BBW-compliant management were much higher for drugs with a drug-disease warning. Rates ranged from 84.7% for metformin and combinations to 90.2% for cilostazol.

Prescriber Compliance With Black Box Warnings

Table 1. Medications With a BBW Selected for Investigation

Medication	Generic Product Identifier Codes	BBW Summary	Definition of BBW Compliance	BBW Release Date
Loop diuretics	372000	Potent diuretics; may lead to dehydration and electrolyte depletion	New users: Claims for serum electrolyte (<i>CPT</i> 80048, 80050, 80051, 80053, 80069, 84550), creatinine (<i>CPT</i> 80048, 80050, 80053, 80069, 82565), and BUN (<i>CPT</i> 80048, 80050, 80053, 80069, 84520) at least once within 3 months of first medication claim, and at least 1 other in 12 months Existing users: At least 1 lab claim as above	Prior to 1996
Metformin and combinations	2799800260 2799700235 2725005000 2799700240	Lactic acidosis (rare but serious)	Not receiving pharmacologic treatment for heart failure, and if ≥ 80 years old, perform creatinine clearance (<i>CPT</i> 82575)	November 1997
Ketoconazole	1140404000 1699000280 5510403500 5510990235 9010990350 9015404500 9630106400	Hepatic toxicity; coadministration with terfenadine, astemizole, and cisapride is contraindicated	New users: Baseline LFT (<i>CPT</i> 80076, 80053, 80050, 84450, 84460) and at least 1 lab claim for LFT within 12 months Existing users: At least 1 LFT within 12 months of index prescription	Prior to 1996
Cyclosporine	994020 8672002000 9646881000 9940202000 9940202030	Increased risk of lymphomas, other malignancies, and infection; may cause hypertension; caution with other nephrotoxic drugs; not interchangeable with other forms of cyclosporine without close monitoring	Rheumatoid arthritis (ICD-9-CM diagnosis 714.0, 714.1, 714.2, 714.9, 720.0): At least 10 serum creatinine tests (<i>CPT</i> 80048, 80050, 80053, 80069, 82565) within 12 months of first cyclosporine fill in 2005 Psoriasis (ICD-9-CM diagnosis 696.0, 696.1): At least 6 labs within 12 months of first cyclosporine fill in 2005 including BUN (<i>CPT</i> 80048, 80050, 80053, 80069, 84520), CBC (<i>CPT</i> 80050, 85025, 85027), serum magnesium (<i>CPT</i> 83735), potassium (<i>CPT</i> 80048, 84132, 80050, 80053, 80051, 80069), uric acid (<i>CPT</i> 84550), and lipids (<i>CPT</i> 80061, 82465, 83718, 84478)	Prior to 1996
Methotrexate	6625005000 6625005010 2130005000 2130005010	Bone marrow, liver, lung, and kidney toxicities; diarrhea and stomatitis; tumor lysis syndrome; skin reactions; and fatal opportunistic infections	Rheumatoid arthritis patients only: (ICD-9-CM diagnosis 714.0, 714.1, 714.2, 714.9, 720.0): New users: Baseline CBC with differential and platelet counts (<i>CPT</i> 80050, 85025, 85027), LFT (80076, 80053, 80050, 84450, 84460), and creatinine (<i>CPT</i> 80048, 80050, 80053, 80069, 82565) at baseline (within 2 months of start) and 5 additional in the year following their first fill Existing users: Five CBCs with differential and platelet counts, LFT, and creatinine within the year following first fill	Prior to 1996

(Continued)

■ **Table 1.** Medications With a BBW Selected for Investigation (*Continued*)

Medication	Generic Product Identifier Codes	BBW Summary	Definition of BBW Compliance	BBW Release Date
Carbamazepine	7260002000	Potentially fatal blood cell abnormalities have been reported following treatment	New users: At least 1 CBC within 6 months before starting treatment and at least once within 12 months following treatment initiation Existing users: At least 1 CBC within 3 months prior to or within 12 months of index prescription	Prior to 1996
Amiodarone HCl	3540000500	Life-threatening arrhythmias; fatal pulmonary toxicity; hepatic toxicity; patient should be hospitalized while administering loading dose	New users: Monitor LFTs (<i>CPT</i> 80076, 80053, 80050, 84450, 84460) at baseline and at 6-month intervals Existing users: Monitor LFTs at least twice within a 12-month interval	Prior to 1996
Cilostazol	8515551600	Contraindicated for use in CHF patients: cilostazol and metabolites are inhibitors of phosphodiesterase III; such activity has been shown to decrease survival of patients with class III-IV CHF; contraindicated in patients with CHF of any severity	No diagnosis of CHF (<i>ICD-9-CM</i> 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9) prior to first fill in 2005	Prior to 1996

BBW indicates black box warning; BUN, blood urea nitrogen; CBC, complete blood count; CHF, congestive heart failure; *CPT*, *Current Procedural Terminology*; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; LFT, liver function test.

DISCUSSION

This study uncovered high rates of prescribing medications regardless of the presence of a BBW and substantial variation in the level of BBW compliance by type of BBW (ie, drug-disease vs drug-laboratory) in the clinical management of Horizon participants age ≥65 years. Compliance with BBWs associated with a drug-disease interaction (ie, metformin and cilostazol) was high. Compliance was much lower for medications with a drug-laboratory BBW.

Our results are consistent with previous research that documented good compliance with drug-disease BBWs.^{2,3} Both of these studies also reported lower rates of prescriber compliance with drug-laboratory BBWs than with drug-disease BBWs.^{2,3} However, the compliance rates for drug-laboratory BBWs observed in our study were notably lower than those previously reported.

Some of these differences can be attributed to the research methods specific to each study and to the fact that the BBW for a single medication can vary by indication and age of the patient. Wagner et al studied individuals from birth to age

>85 years using administrative pharmacy claims to evaluate BBW prescribing.³ The population in the study by Lasser et al included individuals age ≥18 years and used electronic health records.² Our study focused on adults age ≥65 years and used administrative pharmacy and medical claims.

There are several limitations to this study. First, our medical claims may have been incomplete for several reasons. The claims were limited to 3 diagnosis fields, and we could not determine the presence of a specific diagnosis of interest if it were not captured in 1 of these 3 fields. Another reason for incomplete medical claims is that approximately 40% of our sample was enrolled in a plan with a capitated laboratory benefit. In a capitated laboratory benefit, health plans reimburse laboratories participating in their preferred provider network for a predefined and limited number of laboratory tests. Additional laboratory services over the limit are not billed to the health plan; therefore, claims for those services are not captured in the administrative claims database. A third possible explanation for incomplete medical records is that a portion of the Horizon study sample also was concurrently enrolled in Medicare Part B. We were not able to identify patients with Medicare Part

Prescriber Compliance With Black Box Warnings

Table 2. Patients Using Medications With a BBW Who Were Managed According to Operationalized Definitions of Compliance

Medication	Type of BBW	Total No. of Patients	No. (%) of Patients Managed According to Operationalized Definitions of Compliance
Carbamazepine	D-L	659	83 (12.6)
Amiodarone	D-L	2714	96 (3.5)
Ketoconazole	D-L	2797	233 (8.3)
Loop diuretics	D-L	24,525	6110 (24.9)
Methotrexate	D-L	1026	44 (4.3)
Cyclosporine	D-L	153	1 (0.7)
Metformin and combinations	D-D	16,230	13,753 (84.7)
Cilostazol	D-D	1283	1157 (90.2)

BBW indicates black box warning; D-D, drug-disease; D-L, drug-laboratory.

B coverage given the information available to us. As a result, we could neither exclude them from the analysis nor estimate the proportion of our study sample affected by the incomplete data. Furthermore, we were unaware of the participants' complete medical coverage eligibility and assumed the pharmacy coverage (which spanned July 1, 2004, through December 31, 2006) was equivalent to the medical coverage. Another limitation to this analysis was that administrative claims document the procedures and laboratory tests that were performed, not necessarily the procedures and tests that were ordered. Convenience, cost, and other factors may contribute to a patient's decision not to adhere to provider instructions. Finally, the high rates of noncompliant management observed in this study may be related to a provider's evaluation of a patient's prognosis and a weighed assessment of necessary medical care versus ethical treatment under the circumstances.

Prescriber compliance with BBWs is an important issue in the clinical management of older adults because of the potential risk of adverse drug events in this already higher risk population. In general, clinical management of adults age ≥ 65 years is challenging because older adults are more likely to be in poorer health and use more prescription and over-the-counter medications than younger adults.^{4,5} Temporal trends have indicated that the mean number of medications used by older adults is increasing⁶; a concomitant increase in the number of adverse drug events can be anticipated.⁷ For these reasons, compliance with BBWs is a critical component of appropriate patient management, particularly in adults age ≥ 65 years, and a major patient safety issue.

Administrative medical and pharmacy claims data could provide a valuable resource for health plans to conduct periodic surveillance of provider compliance with BBWs. The surveillance goal is timely and targeted educational intervention linked to

continuous improvement in patient safety and quality of care. Although we found that administrative claims tend to overestimate noncompliance with drug-laboratory BBWs, estimates of compliance with drug-disease BBWs are more in line with other published estimates. Our findings also are consistent with those of other studies reporting that provider compliance with BBWs is suboptimal.^{2,3} Medical chart review could be considered the gold standard for monitoring BBW compliance because patient charts include detailed documentation of prescriber behavior. However, medical chart review is both laborious and costly. Electronic health records are an ideal data source for this type of activity, but many private practices and clinics have not yet adopted the technology. Until electronic health records are universally adopted, administrative claims analysis could be a good alternative for monitoring prescriber compliance with BBWs in adults age ≥ 65 years. Chart review could be performed as needed on a case-by-case basis based on the outcome of the claims analysis to more thoroughly investigate any outcome.

CONCLUSION

Administrative claims analysis identified low rates of prescriber compliance with BBWs in managing patients age ≥ 65 years. Until electronic health records are more widely available, we propose that billing data may be an acceptable preliminary resource to evaluate prescriber compliance with BBWs among patients using high-risk medications.

Author Affiliations: From CVS Caremark (JAR), Hunt Valley, MD; CVS Caremark (CC, MCM), Scottsdale, AZ; CVS Caremark (JEB), Northbrook, IL; and Horizon Blue Cross Blue Shield (AM, SAJ), Newark, NJ. Dr Berger is now with Health Intelligence Partners, Chicago, IL.

Funding Source: None reported.

Author Disclosure: Dr Berger reports owning stock in CVS Caremark. The other authors (JAR, CC, MCM, AM, SAJ) report no relationship or fi-

nancial interest with any entity that would pose a conflict of interest with the subject matter of this article.

Authorship Information: Concept and design (JAR, JEB, MCM, AM, SAJ); acquisition of data (JAR); analysis and interpretation of data (JAR, CC, JEB, MCM, AM, SAJ); drafting of the manuscript (JAR); critical revision of the manuscript for important intellectual content (JAR, CC, JEB, MCM, AM, SAJ); statistical analysis (JAR); administrative, technical, or logistic support (CC, JEB, MCM); and supervision (JAR, JEB, MCM).

Address correspondence to: Charmaine Coulen, MPH, CVS Caremark, 9501 E Shea Blvd, Scottsdale, AZ 85260. E-mail: charmaine.coulen@caremark.com.

REFERENCES

1. Specific requirements on content and format of labeling for human prescription drugs. 21 CFR §201.57(e), 4-1-02 edition.
2. **Lasser KE, Seger DL, Yu DT, et al.** Adherence to black box warnings for prescription medications in outpatients. *Arch Intern Med.* 2006;166(3):338-344.
3. **Wagner AK, Chan KA, Dashevsky I, et al.** FDA drug prescribing warnings: is the black box half empty or half full? *Pharmacoepidemiol Drug Saf.* 2006;15(6):369-386.
4. **Zhan C, Sangl J, Bierman AS, et al.** Potentially inappropriate medication use in the community-dwelling elderly: findings from the 1996 Medical Expenditure Panel Survey. *JAMA.* 2001;286(22):2823-2829.
5. **Linton A, Garber M, Fagan NK, Peterson MR.** Examination of multiple medication use among TRICARE beneficiaries aged 65 years and older. *J Manag Care Pharm.* 2007;13(2):155-162.
6. **Linjakumpu T, Hartikainen S, Klaukka T, Veijola J, Kivelä SL, Isoaho R.** Use of medications and polypharmacy are increasing among the elderly. *J Clin Epidemiol.* 2002;55(8):809-817.
7. **Hajjar ER, Cafiero AC, Hanlon TC.** Polypharmacy in elderly patients. *Am J Geriatr Pharmacother.* 2007;5(4):345-351. ■