Proactive Postmarketing Surveillance: Overview and Lessons Learned from Medication Safety Research in the Veterans Health Administration

Robert R. Campbell, JD, MPH, PhD; Andrea M. Spehar, DVM, MPH, JD;
Dustin D. French, PhD

Abstract

This report is an overview of the medication safety studies conducted by the VISN (Veterans Integrated Service Network) 8 Patient Safety Center of Inquiry (PSCI), Tampa, FL, over the past 5 years. The Center has been developing the research capacity to conduct national Veterans Health Administration (VHA) proactive medication safety surveillance studies as part of its research focus on patient falls and mobility issues in elderly veterans. The Center's research findings describe new directions and alternative approaches based on a paradigm shift in how proactive medication safety surveillance can be conducted using the VHA's comprehensive health care utilization data. These studies are primarily hypothesis-generating and enhanced signal-detection studies on a national level. The lessons learned from the Center's studies may help to inform the current Congressional debate on Food and Drug Administration (FDA) legislation Prescription Drug User Fees Act (PDUFA IV) that affects the nature and rigor of U.S. postmarketing drug safety studies.

Introduction

Considerable controversy exists concerning the sufficiency of current programs that ensure the safety of drugs in the U.S. health care system.[1, 2, 3] The U.S. Food and Drug Administration (FDA) has come under increased scrutiny for safety issues associated with approved drugs.[2, 3, 4, 5] The FDA requires drug manufacturers to do extensive safety and efficacy testing of proposed new medications during the approval process.[6] However, after FDA approval, knowledge gaps exist in its postmarketing safety system.[2, 3, 4, 5, 6, 7] These gaps include concerns that the current postmarketing reporting system fails to detect drug safety risks in a timely fashion, challenges in its ability to monitor drug safety in populations that were not included in the drug approval process (e.g., children, pregnant women, and the elderly), and safety issues with off-label medication use.[6] Because of its sophisticated health information technology system, the Veterans Health Administration (VHA) has a unique opportunity and capacity to provide a model system for proactive postmarketing surveillance of medications.

Proactive medication safety surveillance does not necessarily rely on reports of adverse events (AEs) associated with drugs to initiate an investigation.[8] Historically, voluntary spontaneous reporting systems have focused on adverse drug reactions, defined as responses to a drug that are noxious and/or unintended at doses normally used for treatment.[9] The VHA Patient Safety Center of Inquiry (PSCI) in Tampa, FL, has undertaken a series of proactive medication safety surveillance studies that have focused on adverse health outcomes where the literature has identified medications as a risk factor. These studies have used multivariate analyses focused on the adverse outcome as the dependent variable in the study and temporally linked selected medications as an independent variable to the adverse outcome. These AEs included adverse drug reactions and other adverse outcomes, such as fall-related fractures, that occurred while patients were prescribed a category or class of medication.[10] This article provides an overview of these VHA proactive medication safety surveillance studies and discusses the lessons learned from these studies within the context of the current FDA postmarketing surveillance policy debate.

Current U.S. Initiatives

Potential postmarketing medication safety issues in the United States are largely identified by various AE reporting systems.[11] Medication safety incidents are reported to the FDA from several major sources: as manufacturer reports (AEs that result in serious injury and for which a medication error might be a component), direct contact reports (MedWatch),[12] reports from the U.S. Pharmacopeia (USP, e.g., U.S. Pharmacopeia MEDMARX® Program),[13] and the Institute for Safe Medication Practices (ISMP).[14] With other adverse drug event reporting systems (e.g., VHA Patient Safety Reporting System)[15] or mandatory State serious AE reporting systems,[16] events may or may not be reported to the FDA.[17] Commentators have noted that problems with the FDA's postmarketing surveillance program include the need for more population-based data on medication usage and better use of existing data.[7, 18, 19, 20]

Additionally, other issues raised have included the FDA's inability to require and enforce timely clinical studies of postmarketing drug safety, the limitations of the voluntary MedWatch reporting system, and limited resources currently devoted to the FDA's Office of Drug Safety.[1, 7] The recent Institute of Medicine (IOM) study on drug safety underscored that two decades of studies have made recommendations addressing these same deficiencies in drug postmarketing surveillance programs in the United States.[2]

A fundamental recommendation from recent studies of the FDA's postmarketing surveillance system is the need for large-scale health care datasets to conduct population-based safety studies.[2,7] The recent General Accounting Office (GAO) and the IOM reports recommend that the FDA obtain large-scale datasets for postmarketing studies in order to enhance FDA medication safety activities.[1, 2] A major finding of the GAO (2006) report was that the FDA needs to gain access to and analyze large-scale datasets from more diverse patient populations, over a longer period, through a postmarketing safety surveillance system utilizing electronic health care data systems.[1] The FDA has recognized the need for analyses of large-scale health care utilization datasets and has contracted with outside providers—largely managed care organizations and research institutions—to conduct them.[6, 21]

Health care information in the United States is largely fragmented, so the ability to link medications to adverse outcomes of interested is limited. No U.S. organization exists that actively collects and analyzes national, population-based data on the linkage of medication use with a broad range of potential patient harms that span adverse drug reactions, injuries, and other serious medical conditions, such as strokes and acute myocardial infarctions (AMIs). Several countries, the World Health Organization (WHO), and the European Union (EU) have been actively developing more population-based medication safety surveillance systems.[22, 23, 24, 25] These developing international systems are possible because they occur in countries with nationally financed health care systems that have the ability to link pharmacy and health care utilization data.

In recent years, the VHA has conducted postmarketing safety surveillance primarily through several mechanisms. These include an affiliation with the Research on Adverse Drug Events and Reports Project (RADAR),[26] the national VHA Center for Medication Safety,[27] and health services research. The RADAR project, partially funded by the VHA, focuses on identifying, evaluating, and disseminating information concerning serious adverse drug reactions.[26] This project primarily uses clinical event reports from investigators and other clinicians to initiate an investigation and then obtains data from other sources, which may include FDA case reports and literature reviews.[26] The VHA currently has a very robust medication safety program administered by its Pharmacy Benefits Management system (PBM), which conducts drug utilization reviews and maintains the sophisticated national health information technologies associated with its computerized prescribing and barcoded medication administration systems. The VHA's Center for Medication Safety, in conjunction with the National Center for Patient Safety, is responsible for coordinating adverse drug event reporting and medication safety administrative programs.[27]

The VHA health service's research programs have historically supported a broad range of medication safety-related research. Recently, several new PSCIs were established and funded under the auspices of the VHA's National Center for Patient Safety (NCPS). These new Centers will focus their research activities on specific medication safety issues, such as risk assessment of drugs, medication reconciliation, and safer outpatient medication usage. These three new patient safety centers join with the Veterans Integrated Service Network (VISN) 8 PSCI in continuing the VHA's commitment to patient safety research.

Proactive Medication Safety Surveillance Studies at the VISN 8 Patient Safety Center of Inquiry, Tampa, FL

The VISN 8 PSCI was established in 1999 to conduct research on mobility-related safety issues in elderly veterans. It has established an international reputation in the areas of falls and safe patient handling and movement. Because of the recognized chance of certain medications to increase the risk of injurious falls in the elderly, for the past 5 years, the Center has been developing the research capacity for proactive medication safety surveillance studies similar to the Agency for Healthcare Research and Quality's (AHRQ) DEcIDE (Developing Evidence to Inform Decisions about Effectiveness) project.[28]

The DEcIDE project is developing a database that links administrative data with clinical components from the pharmacy, outpatient, inpatient, physician office, and emergency departments.[28] Center studies linking VHA administrative and clinical datasets have demonstrated the utility of using hospital discharge data to develop an injury and AE surveillance system for the VHA.[29] The Center's medication safety research over the last 5 years has produced studies that have examined drug-related adverse outcomes in many care settings.[30, 31, 32, 33, 34, 35, 36, 37, 38] The usefulness of VHA national data for proactive medication safety surveillance, or enhanced pharmacovigilance studies, is based on the ability of researchers to link national data on health care utilization from all VHA datasets across care settings.

Postmarketing medication safety studies have largely relied on spontaneous, passive reporting systems.[2] Spontaneous reporting systems are limited by the fact that clinicians may fail to identify and report illnesses that they suspect are not due to a drug. This has led to the development of systems in other countries (mainly in the EU) based on reporting all AEs in the initial postmarketing period.[39, 40] Proactive medication safety studies, with the proper data and methods of analysis, can be expanded beyond adverse drug reactions and recognized adverse drug-drug or drug-disease interactions to encompass a broader range of patient harms and injuries to provide a more robust, proactive medication safety surveillance system.[29, 34, 38]

These kinds of proactive studies are largely hypothesis-generating and enhanced signal-detection studies that may identify associations between medications and the outcomes of interest over a longer period. However, it must be noted that these studies are primarily aimed at hypothesis testing or enhanced detection of safety signals. These kinds of studies require clinician involvement in their design and interpretation. The ultimate determination of safety issues requires further examination and studies that could include examination of the patients' medical records, consultations with manufacturers, and the involvement of the FDA.

The IOM report recommended that the FDA adopt an approach to drug risk and benefit that extends more comprehensively past the initial approval process.[2] Another recommendation (IOM recommendation 4.3, 2006) was that the FDA collaborate with public and private organizations and use data from publicly funded health care programs, including the Department of Veterans Affairs (VA) and Department of Defense (DoD), to improve the drug safety system with partial public funding.[2] The VA and DoD datasets are components of comprehensive electronic health care data systems. This enhances their ability to rapidly and efficiently identify potential medication-related AEs that might merit further analysis using electronic medical records.

Recently, the Centers for Medicare & Medicaid Services (CMS) also recognized the usefulness of large-scale datasets for postmarketing surveillance in a proposed rule.[41] The rule proposes that the new Medicare Part D claims data be used for a variety of purposes, including postmarketing surveillance activities by the FDA. These surveillance activities, according to the proposed rule, could: (1) include monitoring patterns of drug use in the elderly and the disabled with the goal of identifying unsafe or suboptimal patterns of use, (2) be used to identify rare but serious complications more quickly and effectively, or (3) be used to facilitate formal epidemiologic studies examining the nature and magnitude of risk associated with particular medications.[41]

When linked to Medicare health care utilization data, these Medicare Part D pharmacy claims data could create a more effective postmarketing medication safety surveillance system. Currently, these kinds of proactive postmarketing studies of medications in specific populations—e.g., a larger group of aged patients with chronic diseases and long-term medication usage—are not widely published in the United States.

Lessons Learned from Center Medication Safety Research

The major lessons learned from developing the capacity for VHA proactive medication safety surveillance research are summarized below:

Large scale pharmacy datasets capable of being linked to health care utilization data are critical for identifying groups of patients who were exposed to a particular medication and the effect of that exposure to the health outcome of interest. This is especially important when the outcome of interest is a very rare event. The VHA maintains national pharmacy datasets that include inpatient and outpatient settings of care. In contrast to individual reports of adverse drug reactions, national pharmacy data allow one to put AEs, or health outcomes of interest, into a population-based context. Large-scale pharmacy administrative datasets that include unique patient identifiers can be used to rapidly identify a population of patients exposed to a particular medication of interest. This provides a "denominator" of patients exposed to the drug and a critical context for determining the subsequent effect of the adverse outcome of interest. The Center's studies temporally linked these patients to their health care utilization to see which patients had the AE or outcome of interest. An example of this kind of Center study was the research on COX-2 inhibitor usage linked with hospitalizations for an AMI or stroke.[38]

Proactive medication surveillance systems require detailed information on relatively large numbers of patients who have been prescribed the medication, in addition to comprehensive data on their health care utilization. VHA studies have demonstrated the utility of using clinical datasets to rapidly identify populations exposed to medications of interest to study outcomes of interest that are either relatively common or rare. Without sufficient information on the numbers of potentially affected patients (i.e., a denominator), it is difficult to evaluate the effect on the VHA system of the safety of a medication, especially for very rare AEs. An example is the Center's study of Viagra® use and the potential for patients using the drug to develop ischemic optic neuropathy.[42]

Linked administrative health care data can be used to identify a broader spectrum of adverse outcomes and associated health care utilization costs beyond adverse drug reactions or adverse drug events. These kinds of studies—which represent a major paradigm shift from the current focus of postmarketing safety studies—greatly expand the scope of medication safety surveillance into new areas, where medications themselves are a risk factor for the occurrence or development of an adverse outcome. This is exemplified by the Center's studies of hospitalizations and costs for fall-related injuries temporally linked to the use of psychotropic medications.[29, 30, 32]

These kinds of studies are the logical extension of new initiatives from accreditation activities, such as the Joint Commission's patient safety goals related to medications and fall-risk

assessment. Recent patient safety initiatives have recognized the importance of patient medication assessments in relation to injury risk profiles. An example is The Joint Commission's use of the patient safety goals to accurately and completely reconcile medications across the continuum of care and to reduce the risk of patient harm resulting from falls through assessments that include patients' current medication profiles.[43]

Medication safety surveillance employs epidemiologic methods to identify and analyze potential adverse outcomes associated with the use of medications. Adverse outcomes can encompass more than adverse drug reactions. The FDA has defined pharmacovigilance as "all post-approval scientific and data gathering activities relating to the detection, assessment, understanding, and prevention of AEs or any other product-related problems."[44]

"Pharmacovigilance" is defined in a WHO report as "the science and activities relating to the detection, assessment, understanding, and prevention of AEs or any other possible drug-related problems."[45] Center studies have demonstrated the usefulness of linked datasets to explore the associations of medications with a broader range of AEs, especially in the elderly veteran population.

Proactive medication safety analyses can be used to identify major drug-drug interactions that were associated with AEs temporally and where these interactions were modeled as independent risk factors for adverse outcomes, such as injuries. An example of this kind of Center study is an analysis of concomitant use of benzodiazepines and other medications linked to adverse outcomes, such as fall-related injuries in elderly veterans.[33]

Drug-drug interactions are widely evaluated in drug utilization reviews and in studies of potentially inappropriate prescribing for selected subpopulations.[46, 47, 48] However, few studies have used large-scale, population-based datasets to examine the influence of drug-drug interactions on other relatively common adverse health outcomes, such as fall-related injuries.[31, 32, 33] These types of hypothesis-generating studies also facilitate the identification of rare, or previously unrecognized, serious AEs that can be further investigated, as suggested in the CMS proposed rule related to the potential uses of Medicare Part D prescription data.[41]

The use of large-scale national datasets allows researchers to conduct more sophisticated epidemiologic studies that incorporate multivariate analyses. These kinds of multivariate analyses can inform clinical decisionmaking by empirically specifying the nature and magnitude of the risk of having a particular adverse outcome associated with a medication. The Center's study of benzodiazepines and the risk of injury incorporated a multivariate analysis and provided information to health care providers on the risk of an injury associated with the interaction of benzodiazepine dose and duration, while controlling for other important factors.[31]

By using multivariate models that control for important confounders identified in comprehensive datasets, a more effective postmarketing surveillance system can be developed to protect patients against adverse outcomes and to inform clinical prescribing patterns. Specific information for clinicians, based on empirical research that quantifies the effect of medications on identified risks from more sophisticated multivariate modeling of risk factors, can guide safer prescriptive practices and positively influence patient safety. These kinds of sophisticated

pharmacoepidemiologic studies support the current Federal initiatives for expanded use of Medicare Part D claims data for research recommended in the proposed CMS rule and current AHRQ medication safety research initiatives.[41]

Proactive medication safety studies using population-based datasets can be used to develop medication and comorbidity profiles in the elderly linked to specific injuries or other health outcomes of interest. These kinds of studies can promote safer prescribing practices in elderly subpopulations and care settings. Center studies have demonstrated that analyses can be conducted to produce profiles of patients that include summaries of their medication and comorbidity profiles. These profiles have been included in Center analyses that have examined the association of these patient profiles with outcomes of interest such as treatment for outpatient fractures or inpatient hospitalizations for syncope.[34, 36]

Polypharmacy and multiple chronic diseases are common in the elderly population.[33, 46, 47, 48, 49, 50, 51] Premarketing medication studies typically do not include patients with multiple comorbidities or patients taking multiple medications. Targeted proactive postmarketing surveillance could be especially valuable for these types of vulnerable populations. This is a recognized limitation of the current FDA drug approval process, noted in a recent IOM report (2006), that could be partially addressed by the proposed CMS rule.[2, 41] Medication and comorbidity profiles derived from large-scale datasets permit proactive, hypothesis-generating studies of health care utilization and could lead to safer prescribing practices in specific patient cohorts. Proactive medication safety studies that incorporate medication and comorbidity profiles, a common occurrence in the elderly, would be responsive to the proposed uses of national Medicare Part D prescription data under several Federal research initiatives.[41]

A proactive medication safety surveillance system can be used on a national level to identify adverse outcomes and events in different settings of care that are associated with selected medications. Center studies have examined national data on adverse health outcomes associated with selected medication usage in long-term care, acute care hospitalizations, and outpatient treatment settings.[29, 32, 34, 37]

The CMS proposed rule for sharing Medicare Part D data linked to Medicare Parts A and B data would permit more rapid and effective investigations of medication-related adverse outcomes in different populations and care settings, similar to the Center's research and other VHA research.[41]

Conclusion

The Center's medication safety studies have demonstrated the utility of conducting research using the VHA's national administrative datasets for proactive medication safety surveillance. The Center's studies have been focused on identifying potential medication-related AEs in different care settings and in specific populations. These studies have explored hypotheses about the association between certain medications and selected health outcomes of interest to the Center and the VHA. The studies have demonstrated the utility of these national comprehensive VHA datasets to enhance proactive medication safety surveillance studies and to enhance signal detection for AEs.

The current policy debate about improving the FDA's postmarketing surveillance activities underscores the importance of regulator and researcher access to large-scale health care datasets to conduct research similar to the VHA's studies. The current Congressional debate on the exact kinds of postmarketing safety study provisions to include in the final legislation concerning the Prescription Drug User Fees Act amendments (PDUFA IV) underscores the public interest in providing for more rigorous and timely postmarketing safety studies.[52] Large-scale national datasets, although necessary to identify potential medication-related AEs, are not sufficient for a comprehensive medication safety surveillance system.

More definitive studies of medication safety ultimately require access to information usually available only in medical records. Ideally, these should be electronic medical records similar to the VHA's electronic medical record system. The VHA's comprehensive national programs in postmarketing surveillance have been in place for several years and encompass administrative programs and an extensive array of health services research initiatives.[53] Recently, the VA and the FDA entered into a memorandum of understanding to allow collaborative safety research initiatives capitalizing on the richness of the VHA's national datasets and expertise.[54]

Many safety research initiatives are currently underway that can inform the direction of the FDA postmarketing surveillance debate in Congress. These include the VHA programs, drug safety surveillance programs in other countries, and health services research being conducted in numerous sites across the United States. The current AHRQ medication safety research initiatives under the DEcIDE program constitute a promising avenue of Federally supported health research in the effectiveness of health care services. Health care systems, providers, and insurers have important contributions to make to the current FDA policy debate based on their own internal data systems and medication safety program initiatives. Medication safety, cost, and effectiveness studies will continue to be important public policy concerns as the Medicare Part D drug prescription program matures in the coming years. New directions and alternative approaches in postmarketing surveillance studies will continue to be an important area for future health services research.[55]

Acknowledgments

The research reported here was supported by the Department of Veterans Affairs, Veterans Health Administration (VHA). The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.

Author Affiliations

VISN-8 Patient Safety Center of Inquiry, Tampa, FL.

Address correspondence to: Robert R. Campbell, JD, MPH, PhD, VISN-8 Patient Safety Center of Inquiry, 11605 North Nebraska Avenue (118M), Tampa, FL 33612; telephone: 813-558-3962; fax: 813-558-3990; e-mail: robert.campbell3@va.gov.

References

1. Drug safety: Improvement needed in FDA's postmarket decision-making and oversight process. Report No.: GAO-06-402; Washington, DC: US Government Accountability Office; 2006 March.
2. Baciu A, Stratton K, Burke SP, eds. The future of drug safety: Promoting and protecting the health of the public. Committee on the assessment of the U.S. drug safety system, Board on Population Health and Public Health Practice. Washington, DC: Institute of Medicine; 2006.
3. Sibbald B. Rofecoxib (Vioxx) voluntarily withdrawn from market. CMAJ 2004; 17: 1027-1028.
4. Grassley C, Baucus M, Graham D, et al. FDA, Merck and Vioxx: Putting patient safety first? United States Senate Committee on Finance; 2004. Available at: news.public.findlaw.com/hdocs/docs/vioxx/111804vioxxhrngs.html. Accessed April 10, 2008.
5. Carpenter D, Ting MM. Essay: The political logic of regulatory error. Nat Rev Drug Discov 2005; 4: 819-823.
6. Report to the nation: Improving public health through human drugs. Rockville, MD: U.S. Food and Drug Administration (FDA), Center for Drug Evaluation and Research (CDER); 2005.
7. Gottlieb S. Opening Pandora's pillbox: Using modern information tools to improve drug safety. Health Aff (Millwood) 2005; 24: 938-948.
8. Pharmacovigilance planning: Planning of pharmacovigilance activities. Report No.: CPMP/ICH/5716/03. London: The European Agency for the Evaluation of Medicinal Products (EMEA); Report No.: CPMP/ICH/5716/03; 2003 November 20.
9. International drug monitoring: The role of national centres. Technical Report Series No 498. Geneva, Switzerland; World Health Organization; 1972.
10. Aronson JK, Ferner RE. Clarification of terminology in drug safety. Drug Saf 2005; 28: 851-870.
11. Smetzer JL, Cohen MR. Medication error reporting systems. In: Medication errors. 2nd ed. Washington, DC: American Pharmacists Association; 2006.
12. U.S. Food and Drug Administration (FDA). MedWatch; 2006. Available at: www.fda.gov/medwatch/. Accessed April 14, 2008.
13. United States Pharmacopeia (USP). MEDMARX®. Rockville, MD: U.S. Pharmacopeia; 2006. Available at: www.usp.org/products/medMarx/. Accessed April 14, 2008.
14. U.S. Pharmacopeia (USP) and the Institute for Safe Medication Practices (ISMP) USP-ISMP Medication Errors Reporting Program (MERP); 2006. Available at: www.usp.org/hqi/patientSafety/mer/. Accessed April 14, 2008.
15. Department of Veterans Affairs (VA). Patient safety reporting system. Patient Safety Resources: National Center for Patient Safety; 2006. Available at: www.va.gov/ncps/. Accessed April 14, 2008.
16. Rosenthal J, Booth M. Maximizing the use of State adverse event data to improve patient safety. Portland, ME: National Academy for State Health Policy; 2005.
17. Aspden P, Wolcott J, Bootman JL, et al, eds. Preventing medication errors: Quality chasm series. Committee on Identifying and Preventing Medication Errors. Washington, DC: Institute of Medicine; 2006.
18. Lenzer J. U.S. government agency to investigate FDA over rofecoxib. Br Med J 2004; 329: 935.
19. Rodriguez EM, Staffa JA, Graham DJ. The role of databases in drug postmarketing surveillance. Pharmacoepidemiol Drug Saf 2001; 10: 407-410.
20. Avorn J. Powerful medicines: The benefits, risks, and costs of prescription drugs. New York: Alfred A. Knopf: Distributed by Random House; 2004.
21. FDA awards contracts on databases of adverse effects of marketed drugs ability to monitor approved drugs enhanced. FDA Talk Paper #T05-30. Rockville, MD: Food and Drug Administration; 2005 October 7. Available at: www.fda.gov/bbs/topics/answers/2005/ans01368.html. Accessed April 14, 2008.
22. Assessment of the European community system of pharmacovigilance. Karlsruhe, Germany: Fraunhofer Institute for Systems and Innovation Research; Service Contract No: FIF.20040739; 2006 January 25.
23. Practical pharmacovigilance. In: WHO Collaborating Centre for International Drug Monitoring. Uppsala, Sweden: The Uppsala Monitoring Centre; 2006.
24. de Vries F, de Vries C, Cooper C, et al. Reanalysis of two studies with contrasting results on the association between statin use and fracture risk: The general practice research database. Int J Epidemiol 2006; 35: 1301-1308.
25. Paterson JM, Laupacis A, Bassett K, et al. Using pharmacoepidemiology to inform drug coverage policy: Initial lessons from a two-province collaborative. Health Aff (Millwood) 2006; 25: 1436-1443.
26. Bennett CL, Nebeker JR, Lyons EA, et al. The Research on Adverse Drug Events and Reports (RADAR) project. JAMA 2005; 293: 2131-2140.

27. National Center for Patient Safety. Department of Veterans Affairs (VA); 2006. Available at: www.va.gov/ncps/. Accessed April 10, 2008.

28. Medicare prescription drug data development: Methods for improving patient safety and pharmacovigilance using observational data. DEcIDE Projects in Progress; Rockville, MD: Agency for Healthcare Research and Quality; 2006.

29. Campbell R, Bradham D, Sanchez-Anguiano A, et al., eds. Developing a VHA Serious Injury Surveillance System. Advances in patient safety: From research to implementation. Rockville, MD: Agency for Healthcare Research and Quality; 2005. Available at: www.ahrq.gov/downloads/pub/advances/vol1/Campbell.pdf. Accessed April 10, 2008.

30. French D, Spehar A, Campbell R, et al. Outpatient benzodiazepine prescribing, adverse events, and costs. Advances in patient safety: From research to implementation. Rockville, MD: Agency for Healthcare Research and Quality; 2005. Available at: www.ahrq.gov/downloads/pub/advances/vol1/French.pdf. Accessed April 10, 2008.

31. French DD, Campbell R, Spehar A, et al. Benzodiazepines and injury: A risk adjusted model. Pharmacoepidemiol Drug Saf 2005; 14: 17-24.

32. French DD, Campbell R, Spehar A, et al. Outpatient medications and hip fractures in the United States: A national veterans study. Drugs Aging 2005; 22: 877-885.

33. French DD, Chirikos TN, Spehar A, et al. Effect of concomitant use of benzodiazepines and other drugs on the risk of injury in a veterans population. Drug Saf 2005; 28: 1141-1150.

34. French DD, Campbell R, Spehar A, et al. National outpatient medication profiling: Medications associated with outpatient fractures in community-dwelling elderly veterans. Br J Clin Pharmacol 2007; 63: 238-244.

35. French DD, Campbell R, Spehar A, et al. Drugs and falls in community-dwelling older people: A national veterans study. Clin Ther 2006; 28: 619-630.

36. French DD, Campbell R, Spehar A, et al. National Veterans Health Administration hospitalizations for syncope compared to acute myocardial infarction, fracture, or pneumonia in community-dwelling elders: Outpatient medication and comorbidity profiles. J Clin Pharmacol 2006; 46: 613-619.

37. French DD, Campbell RR, Spehar AM, et al. How well do psychotropic medications match mental health diagnoses? A national view of potential off-label prescribing in VHA nursing homes. Age Ageing 2007; 36: 107-108.

38. French DD, Spehar A, Campbell R, et al. A medication surveillance system model to improve patient safety: A national veterans study of cyclooxygenase 2 inhibitors and risks of stroke or myocardial infarction. J Patient Saf 2006; 2: 78-82.

39. Coulter D. PEM in New Zealand. In: Mann R, Andrews E, eds. Pharmacovigilance. Chichester, UK: Wiley & Sons; 2002.

40. Shakir S. PEM in the UK. In: Mann R, Andrews E, eds. Pharmacovigilance. Chichester, UK: Wiley & Sons; 2002.

41. Center for Medicare & Medicaid Services (CMS). Medicare Program; Medicare Part D data, Proposed Rule. Federal Register 2006; 71: 61445-61455.

42. Margo C, French D. Ischemic optic neuropathy in male veterans prescribed phosphodiesterase-5 inhibitors. Am J Ophthalmol 2007; 143: 538-539.

43. Facts about the 2007 National Patient Safety Goals. Oakbrook Terrace, IL: Joint Commission on Accreditation of Healthcare Organizations. Available at: http://www.jointcommission.org/PatientSafety/NationalPatientSafetyGoals/07_npsg_facts.htm. Accessed April 10, 2008.

44. Risk assessment of observational data: Good pharmacovigilance practices and pharmacoepidemiologic assessment. Concept paper. Rockville, MD: U.S. Food and Drug Administration; 2003 March 3; Docket number 02N-0528.

45. The safety of medicines in public health programmes: Pharmacovigilance an essential tool. Geneva, Switzerland: World Health Organization; 2006. ISBN 92 4 159391 1 (NLM classification: QV771). Available at: www.who.int/medicines/areas/quality_safety/safety_efficacy/Pharmacovigilance_B.pdf. Accessed April 10, 2008.

46. Zhan C, Correa-de-Araujo R, Bierman AS, et al. Suboptimal prescribing in elderly outpatients: Potentially harmful drug–drug and drug–disease combinations. J Am Geriatr Soc 2005; 53: 262-267.

47. Hanlon JT, Lindblad CI, Hajjar ER, et al. Update on drug-related problems in the elderly. Am J Geriatr Pharmacother 2003; 1: 38-43.

48. Allard J, Hebert R, Rioux M, et al. Efficacy of a clinical medication review on the number of potentially inappropriate prescriptions prescribed for community-dwelling elderly people. CMAJ 2001; 164: 1291-1296.

49. Lindblad CI, Hanlon JT, Gross CR, et al. Clinically important drug-disease interactions and their prevalence in older adults. Clin Ther 2006; 28: 1133-1143.

50. Perucca E, Berlowitz D, Birnbaum A, et al. Pharmacological and clinical aspects of antiepileptic drug use in the elderly. Epilepsy Res 2006; 68 (Suppl 1): S49-S63.

51. French D, Campbell R, Spehar A, et al. How well do psychotropic medications match mental health diagnoses? A national view of potential off-label prescribing in VHA nursing Homes. Age Ageing 2007; 36: 107-112.

52. FDA letters transmitted to Congress, March 16, 2007 concerning prescription drug users fees amendments 2007 (PDUFA IV). Available at: www.fda.gov/oc/pdufa/default.htm. Accessed April 10, 2008.

53. Campbell R, French D, Cunningham F. Enhancing post-marketing surveillance: Lessons from the Veterans Health Administration. Presentation at the 3rd Annual Harvard FDA Compliance symposium. Boston, MA. August 24, 2007. Powerpoint presentation available at: www.ehcca.com/presentations/fdasymposium3/campbell_4.ppt. Accessed April 10, 2008.

54. Memorandum of understanding between the Food and Drug Administration and the Veterans Health Administration, Department of Veterans Affairs. MOU number 225-07-4300; 2007 January. Available at: www.fda.gov/oc/mous/domestic/225-07-4300.html. Accessed April 10, 2008.

55. Developing Evidence to Inform Decisions about Effectiveness: The DEcIDE Network: Request for Proposals; 2005 July. Rockville, MD: Agency for Healthcare Research and Quality. Available at: www.ahrq.gov/fund/contarchive/rfp050010.htm. Accessed April 10, 2008.