Monitoring adverse drug reactions across a nationwide health care system using information technology

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Purpose. The improvement and linkage of two Department of Veterans Affairs (VA) databases for monitoring adverse drug reactions (ADRs) are described, with a discussion of the potential implications for improved medication safety within the VA health care system.

Summary. Before 2007, VA had limited capability to track and evaluate ADRs across its nationwide network of health care facilities. Since then, VA has established a standardized monitoring system that has improved the reporting, analysis, and trending of ADRs reported by providers and pharmacists at individual VA facilities. The enhanced system has two components with distinct but complementary functions: the Adverse Reaction Tracking database, which is derived by extracting text-based, patient-specific information entered into the VA electronic medical record system by clinicians at the point of care; and the VA Adverse Drug Event Reporting System (VA ADERS), an external web-based portal that contains aggregated data from 146 VA facilities, with standardized coding of reported events. Both databases allow for ADR reporting at the local, regional, and national levels. The VA ADERS database permits rapid electronic reporting of certain ADRs to the federal MedWatch program. The two databases can be used in tandem for more comprehensive assessments of ADR patterns and reporting rates and to generate a wide range of benchmarking data.

Conclusion. In recent years, the refinement of two databases for ADR reporting has increased VA's capability to systematically monitor, track, and report ADRs across its national network of health care facilities. Linking the two databases has further strengthened those capabilities, enhancing medication safety practices and aiding in pharmacovigilance.

Index terms: Databases; Department of Veterans Affairs; Drugs, adverse reactions; Information; Quality assurance; Records; Technology

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An adverse drug event (ADE) is an injury resulting from the use of a drug.[1] This umbrella term encompasses all harms caused by a drug, including those intrinsic to the active pharmaceutical product (e.g., adverse drug reactions [ADRs], allergies) or due to the manner in which the drug is used, whether appropriate or inappropriate (e.g., overdoses). While the ADE construct covers the universe of harms that can result from drug therapy, for most clinicians the most relevant terminology is that pertaining to ADRs, which encompass various adverse effects, including allergic and pharmacologic reactions, that typically occur when a drug product is prescribed at doses

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normally used for treatment[1,2] (the types of ADEs most likely to be encountered in clinical practice).

While ADRs are common[3,4] and ADEs are often preventable or ameliorable,[3-5] they are also underrecognized and underreported.[6,7] In addition, aside from the Food and Drug Administration (FDA) Adverse Event Reporting System (AERS), few comprehensive compilations of reported ADRs exist. Thus, there is a need to improve both the reporting and the systematic compilation of data on ADRs in order to improve the ability of health care systems and oversight groups to identify cases and to assess emerging ADRs associated with specific drugs or occurring in specific patient populations.

The Department of Veterans Affairs (VA) oversees a national health care system that treated over 5.7 million unique patients in fiscal year 2009.[8] Until recently, the VA health care system did not have the systematic capability to monitor and assess ADRs nationally. Since 2007, the VA has developed two methods for extracting and collating ADRs into national databases; these databases provide new analytic tools to potentially improve medication safety practices within the VA health care system.

One of the two national VA databases is derived from extracting patient-specific information entered by health care providers into the Adverse Reaction Tracking (ART) package, a specific part of the VA's electronic medical record. The ART file stores basic information on ADRs, and the electronic medical record (specifically, the medication order-entry system) uses this information during the electronic prescribing process to generate patient-specific order checks, or drug alerts, for prescribers. Locally entered ART data from all VA facilities are now automatically extracted to populate a national database of all ART entries associated with an ADR.

In addition, Veterans Health Administration (VHA) Directive 2008-059, "Adverse Drug Event Reporting and Monitoring," requires VA facilities to report certain ADRs into a second database, the VA Adverse Drug Event Reporting System (VA ADERS).[9] Unlike the ART package, the VA ADERS is external to the electronic medical record and the electronic prescribing process. It does not trigger order checks at the time of prescribing. This intranet-based reporting system allows all facilities to report selected ADRs and stores those reports in a centralized database. ADRs reported by 146 facilities are stored in the database. The reporting system provides greater detail than ART data, with a focus on newly recognized ADRs, and catalogues these ADRs using a standardized coding system, allowing for rapid analysis and tracking of clinically relevant outcomes. The additional functionality of the VA ADERS also allows the direct submission of ADR reports to the FDA MedWatch program and the FDA Vaccine Adverse Event Reporting System.

In this article, using a conceptual framework of ADR recognition and reporting, we discuss the capabilities of the two VA electronic ADR reporting systems and databases. We also discuss how these databases can be used individually and in tandem and how they can be linked into the larger pharmacy benefits management package to enable a more robust understanding of ADR reporting and monitoring. Finally, we highlight the implications of having these databases for improving the accuracy and tracking of ADRs across the VA health care system and for indentifying the need for system-based changes to prevent ADRs and facilitate the reporting of relevant reactions to FDA. For the purposes of this article, the data represent a static snapshot of reports entered into the databases from March 2007 to March 2010.

Conceptual framework

As in any health care system, VA providers and facilities typically take a number of steps in order to help ensure the discovery, accurate documentation, and reporting of ADRs; Figure 1 illustrates the overall process of ADR reporting within the VA system. The pyramid structure reflects the practical notion that as reporting moves upward, there is a decrease in the number of reports, with some of this diminution occurring by design and some due to gaps in accuracy or flaws in the recognition and reporting processes. Each step is described briefly below.

ADR recognition. The recognition of an ADR typically occurs during a provider–patient interaction (e.g., a hospitalization or a clinic visit). Providers may identify an adverse reaction on the basis of a patient's self-report, physical findings, or abnormal laboratory test values. In some cases, the recognition of an ADR may take place via more systematic assessments such as medication-utilization reviews, a search for "trigger drugs" (i.e., certain drugs associated with known adverse reactions), nursing reports, and therapeutic drug monitoring. As is already known, the recognition of adverse reactions may be inexact if the resulting symptoms are nondescript or overlap with those of a comorbid condition.[6,7] In addition, underrecognition may occur if the adverse effect was previously unknown or rare or if the clinician is unaware that a symptom is associated with the use of a drug.

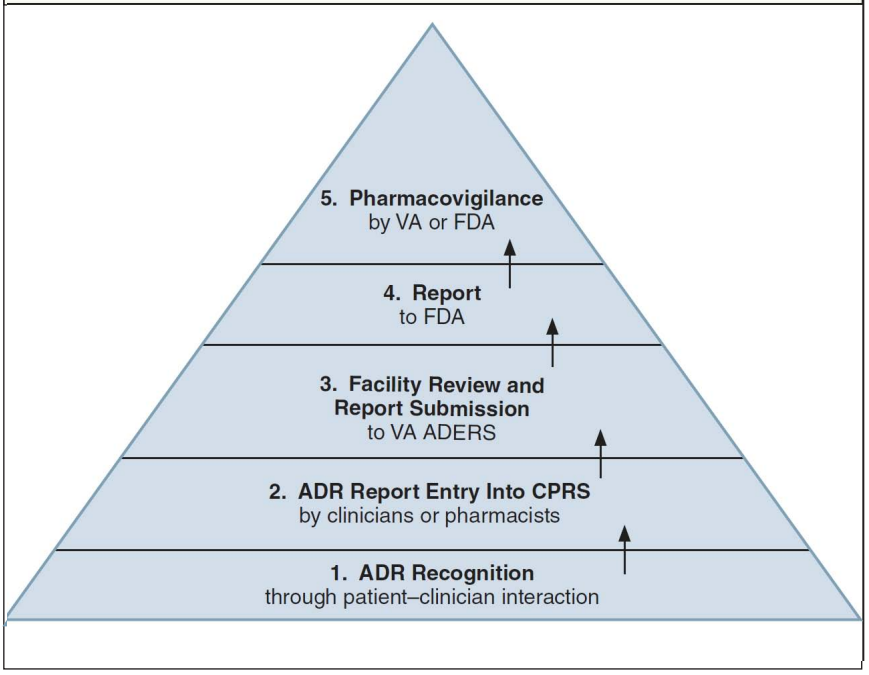
ADR entry into the electronic medical record. The VA electronic medical record is the Computerized Patient Record System (CPRS). Within the CPRS, there is a provider-order-entry system for prescribing medications; in addition, clinical decision-support systems include embedded order checks.[10] For order checks to trigger properly, previous ADRs and allergies must be entered into the electronic record by provid-

ers at the point of care (i.e., an outpatient visit or an inpatient admission). The ART package stores the information and generates allergy and ADR order checks. Figure 2 depicts the ART template for documenting an allergy or ADR in the electronic medical record.

Typically, events are entered in the ART package by clinicians or pharmacists and categorized according to a previously developed VA classification scheme as either "observed" or "historical." The VHA directive defines an observed event as a reaction that is directly observed or occurs while the patient is receiving the suspected causative agent; the term typically refers to a newly noted adverse outcome (generally, one occurring within the preceding three months). Although the term implies that the provider of record made the diagnosis or observed the adverse outcome, the fact that a provider might not have actually "seen" an event does not preclude its classification as observed.[9] Observed events are further classified by severity (i.e., mild, moderate, or severe), and textual information on signs and symptoms is entered via a pulldown menu; the template also allows for elaborative or explanatory comments. The VHA directive defines an historical event as (1) an event occurring more than three months previously or (2) an event that reportedly occurred in the past in another health care setting but no longer requires intervention.[9] Notably, the system order checks will send an alert regardless of whether a drug reaction is listed as observed or historical. As discussed below, the locally inputted ART entries are now automatically extracted and compiled in a larger national database.

VA ADERS. A web-based application for standardizing and centralizing ADR data on observed reactions, VA ADERS is external and not directly linked to the electronic medical record; it does not trigger drug alerts. Reporting is typically done by a designated pharmacist or pharmacists at a given facility. By design, reports entered into the VA ADERS are more detailed and comprehensive than ART entries. Additional information on each reaction includes the probability of the particular drug causing the observed reaction, as determined using the algorithm of Naranjo et al.[11]; the potential preventability of the reaction; and, as in the ART package, the suspected mechanism of the reaction (e.g., pharmacologic, idiosyncratic). Unlike event classification with the ART package, ADRs in the VA ADERS are automatically coded using the *Medical Dictionary for Regulatory Activities (MedDRA) Version 13.0.*[12] Due to the additional effort needed to enter and more fully describe adverse reactions, VHA requires the reporting of only observed events to the VA ADERS[9]; thus, while the VA ADERS database contains fewer reported ADRs, those ADRs are documented with greater detail and a greater degree of coding standardization than can be achieved with the ART package.

Figure 1. Pyramid representation of the chain of allergy and adverse drug reaction (ADR) reporting within the Department of Veterans Affairs (VA) health care system. FDA = Food and Drug Administration, ADERS = Adverse Drug Event Reporting System, CPRS = Computerized Patient Record System.



FDA reporting. Using the VA ADERS application, a reporter (typically a designated pharmacist from a given facility) has the option to submit an ADR report directly to the FDA MedWatch program via an automated facsimile. Automated alerts prompt reporters to submit a report to FDA on events associated with drugs that have been on the market for three years or less, regardless of the reaction's severity. For all other drugs, reporters are instructed to submit FDA MedWatch reports for severe reactions (e.g., life- or organ-threatening effects), as well as any other reaction the reporter deems appropriate to report.

Pharmacovigilance. In a general sense, the term *pharmacovigilance* refers to evaluations to assess, discover, and confirm ADEs across populations.[2] While there are various

methods of achieving those ends, one standard method is to assess spontaneously and voluntarily reported events using information from databases generated through passive surveillance activities such as those conducted by VA or FDA.

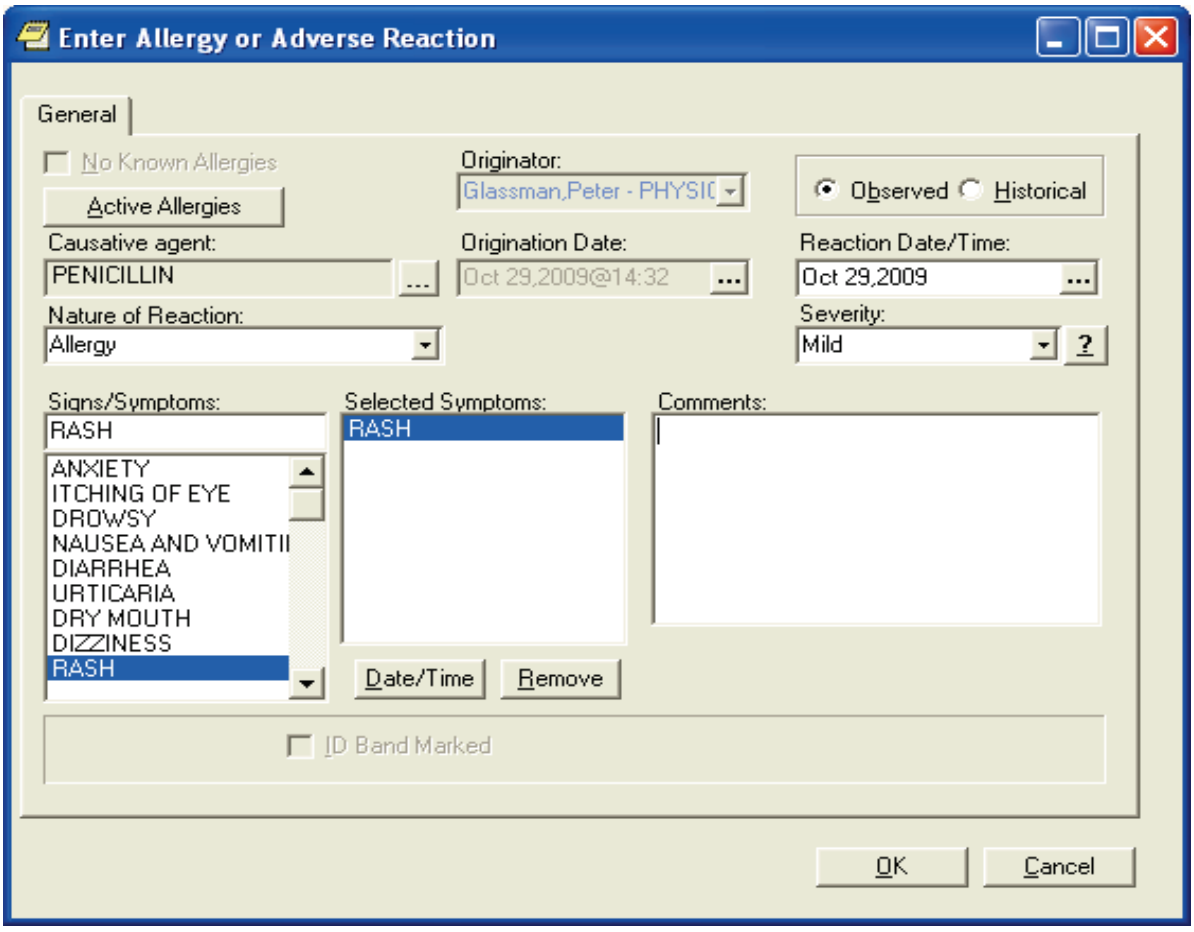
Infrastructure development

The ART database represents the universe of all provider-documented ADRs from all the electronically entered patient-based entries across the entire VA system. ART entries are extracted monthly from each facility by an automated software program.[13] The national database receives over 50,000 entries of allergies and adverse reactions from VA facilities every month. Table 1 illustrates the number of observed and historical ART entries from January 2008 to December 2010.

Since March 2007, the VA ADERS has been used for reporting and aggregating detailed information on observed ADRs that occur across the VA health care system. A key element of the design of the VA ADERS was accessibility to standardized report information to allow for data aggregation and analysis in a timely manner. Using a combination of automated and manual processes, information in the database is standardized each business day; this includes *MedDRA* coding, which allows for more rapid categorization and case searchability than text-based fields (as are used in the ART package). As a result, VA ADERS report data are available for analysis one business day after a report is submitted. Overall, as of the second quarter of fiscal year 2010 (January–March 2010), the database included information on over 1,300 unique drugs and 148,000 associated ADRs (Figure 3).

Before implementing the web-based VA ADERS in March 2007, VA used the legacy Adverse Drug Event System for reporting all serious ADRs. The legacy system required the use of a labor-intensive, manual process to code reports; hence, the reporting of only serious ADRs was mandated. The streamlined proc-

Figure 2. Screenshot of the Adverse Reaction Tracking application within the Computerized Patient Record System showing a completed entry for a suspected penicillin-related event.



esses enabled by the VA ADERS improved the efficiency of ADR coding and the reporting of both serious and nonserious ADRs. The total number of ADRs reported in the legacy database, which was in place from fiscal year 2001 to fiscal year 2006, was approximately 21,000. After the implementation of the VA ADERS in the third quarter of fiscal year 2007, the number of reports increased substantially and totalled over 148,000 as of the end of the second quarter of fiscal year 2010. Thus, over seven times as many reports were submitted to the VA ADERS than had been submitted to the legacy database over a time period roughly twice as long.

The VA ADERS is used for several purposes, including the generation of standardized summary reports, the submission of recommended system changes, surveillance, and benchmarking.

The data reported in the VA ADERS facilitates the benchmarking of ADRs across the VA system by facility or region. Standardized reports on topics such as the top 10 ADRs, the top 10 drugs related to ADRs, the number of ADRs reported with the use of new drugs, and ADRs reported to FDA's MedWatch program are tracked and reported nationally on a quarterly basis. As an example, the top 10 primary-suspect drugs at the national level can be compared with the top 10 primary-suspect drugs within 1 or more of the 21 geographic regions of the VA health care system (Table 2). This tool can be used to review and evaluate regional differences in reporting. Other summary reports can be used to assess events coded as preventable or to evaluate the suspected causes of ADRs (e.g., pharmacology of a drug, drug–drug interaction, idiosyncratic mechanism).

In addition to the standardized reports, ad hoc evaluations and reports can be developed. For example, a review of serious ADRs associated with various i.v. iron preparations led to the removal of high-molecular-weight iron dextran from the VA formulary, and VA's ongoing review of varenicline-associated ADRs has informed VA policy decisions on smoking-cessation aids. In addition, in response to requests regarding specific ADRs, findings are often shared with FDA.

Linking the two databases

By linking the ART and VA ADERS databases, VA can provide more comprehensive assessment and tracking of ADRs from the point of entry into the CPRS (through the ART package) to the reporting of a specific reaction to FDA (through the VA ADERS). As can be seen in Table 3, there is a decrease in the number of reports at each higher level of the chain of reporting. This is expected, because the ART package should contain all entries (observed and historical) while the VA ADERS should contain the subset of observed reactions only; reports to the MedWatch system are fewer still, since only observed reactions that meet FDA requirements are to be reported. However, it is unclear to what extent the decline in reports might reflect gaps in the reporting chain or lost opportunities for reporting higher up in the chain of reporting. For example, a gap might occur when an observed reaction documented within the ART database is not reported to the

Table 1.
Extracted Entries from Adverse Reaction Tracking Database on Events Throughout Veterans Affairs Health Care System[a,b,c]

	2008 ADR Entries		2009 ADR Entries		2010 ADR Entries	
Month	Historical	Observed	Historical	Observed	Historical	Observed
Jan	60,676	2,517	57,641	5,462	56,158	4,677
Feb	55,332	2,408	54,278	4,903	55,386	4,742
Mar	57,212	2,393	61,838	5,936	66,131	5,885
Apr	64,392	2,732	58,371	5,511	63,271	5,448
May	55,632	2,501	54,307	5,234	58,435	5,219
Jun	59,438	2,319	60,115	5,513	62,587	5,627
Jul	56,384	2,643	59,256	5,578	59,695	5,425
Aug	54,345	2,355	60,748	5,815	64,415	6,072
Sep	55,984	2,759	59,346	5,666	63,227	5,167
Oct	55,613	4,935	59,593	5,187	61,183	4,914
Nov	47,844	4,253	54,747	5,164	58,319	4,488
Dec	53,140	4,653	56,779	5,117	56,833	4,678

[a]ADR = adverse drug reaction.
[b]An historical ADR is defined as a reaction that (1) occurred more than three months previously or (2) reportedly occurred in the past in another health care setting but no longer requires intervention.
[c]An observed event is defined as a reaction that is directly observed or occurs while the patient is receiving the suspected causative agent.

VA ADERS or when a MedWatch-eligible report is not submitted to FDA. Another lost opportunity can occur when an observed reaction is misclassified as historical, as such an event will not likely be reported to the VA ADERS or FDA.

In order to begin to address these potential shortcomings, in October 2009 a new feature was added to the VA ADERS to identify ART entries of observed events that were not being reported to the VA ADERS. In addition, entries of observed events in ART can be preloaded into the VA ADERS as draft reports; individual VA facilities can then use those draft reports, completing them (or removing them) as appropriate.

Discussion

Databases of spontaneously reported ADEs, such as those currently used by VA and FDA, have provided a standard for postmarketing surveillance and are a cornerstone of medication safety analyses. They are crucial for monitoring and tracking ADRs across health care systems and populations, and they also provide preliminary information for pharmacoepidemiologic analyses and studies. VA's two ADR databases provide an enormous amount of information and are complementary as well as additive. The ART package provides modest amounts of text-based general information on adverse reactions, as entered into the

Figure 3. Adverse drug reactions entered into Veterans Affairs (VA) Adverse Drug Event Reporting System (VA ADERS) and Food and Drug Administration MedWatch submissions, by quarter.

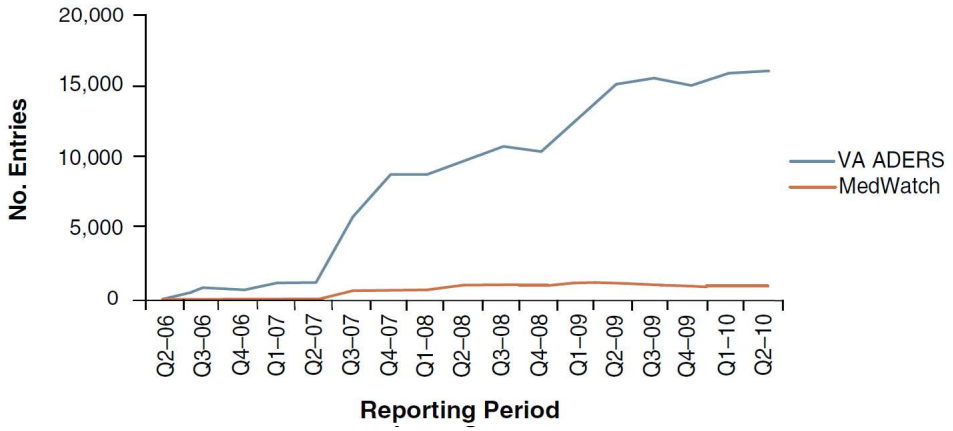


Table 2.
Top 10 Primary-Suspect Drugs Listed in Reports to the Veterans Affairs (VA) Adverse Drug Event Reporting System, Nationwide and by Selected VA Region[a]

Rank	Nationwide	Region A	Region B	Region C
1	Lisinopril	Lisinopril	Lisinopril	Lisinopril
2	Simvastatin	Simvastatin	Simvastatin	Simvastatin
3	Terazosin	Hydrochlorothiazide	Terazosin	Terazosin
4	Warfarin	Terazosin	Niacin	Amlodipine
5	Pravastatin	Sulfamethoxazole–trimethoprim	Lovastatin	Hydrochlorothiazide
6	Hydrochlorothiazide	Rosuvastatin	Hydrochlorothiazide	Sulfamethoxazole–trimethoprim
7	Rosuvastatin	Penicillin	Rosuvastatin	Morphine
8	Niacin	Niacin	Warfarin	Gabapentin
9	Amlodipine	Pravastatin	Pravastatin	Doxazosin
10	Sulfamethoxazole–trimethoprim	Amlodipine	Hydrochlorothiazide–lisinopril	Rosuvastatin

[a]Quarter 2 of fiscal year 2006 to quarter 2 of fiscal year 2010.

VA electronic health record. The VA ADERS yields detailed clinical information with coded clinical outcomes and allows facilities to automatically submit selected event reports to FDA. To our knowledge, no other health care system has developed a comparable level of ADR report integration and monitoring capability. The current use and potential further development of these databases are discussed below.

New benchmarking capabilities. Comparative analyses can assist VA facilities in assessing their own reporting performance, hopefully with the goal of improving rates of reporting of ADRs in general and MedWatch-reportable ADRs in particular. While optimal target rates of ADR reporting across the VA health care system have not been delineated, the published literature suggests that health care providers routinely underdocument and underreport ADRs.[6,7] Standardized reports with normalized data allow for relative comparisons, particularly among similarly sized and situated VA facilities. For example, if facility A enters 50 ADR reports per 1000 unique patients per quarter while facility B, which is similar to A, enters only 5 ADR reports per 1000 patients per quarter, that 10-fold disparity might suggest that the rate of report entry at facility B is not optimal. Ideally, comparative analyses across VA facilities or regions that highlight differences between higher- and lower-reporting facilities will eventually lead to the identification of pharmacotherapy best practices and better estimates of reasonable target ranges for the documentation of reportable ADRs.

In our view and in our experience, two major issues underlie the suboptimal reporting of ADRs within the VA system. First, as discussed previously, clinicians may not recognize adverse reactions. While the extent of the failure to recognize ADRs is largely unknown, one single-site study in an outpatient ambulatory care setting suggested that it occurs frequently, with significant ADRs occasionally overlooked.[6] Another possible contributor to the underreporting of ADRs is the nonentry of recognized events into the appropriate database. The entry of ADR information, typically done by the treating clinicians or pharmacists, is vital for patient safety because it triggers related allergy–drug order checks. Hence, improving this process not only increases relevant order checking but also increases the pool from which facilities draw reportable ADRs.

A quality-improvement tool. Cross-referencing the ART and VA ADERS databases can assist with the improvement of reporting rates by identifying gaps in the reporting chain. For example, if the ART database lists 100 observed events in a given month but the VA ADERS database contains only 50, there is a sizable gap in reporting; that gap will, in turn, hinder reporting to the FDA MedWatch program, as well as VA's ability to track and monitor ADRs across the veteran population. Similarly, if there are events reported to the VA ADERS that should be reported to FDA but are not, this represents yet another gap in the reporting chain. Our hope is that by illustrating gaps in current reporting processes, individual VA facilities will address those gaps and reporting to both the VA ADERS and (as applicable) the FDA MedWatch program will increase.

Reducing ADR classification errors. Integrating the ADR data management systems may improve the accuracy of entries into the local electronic health record and improve the rates of reporting of misclassified adverse reactions. More specifically, the national ART package extraction can be linked with patient-level prescribing information to provide information on potential errors in the classification of historical and observed reactions. This is done by linking an ART report of an historical event with the presence (or absence) of a previous medication prescription from VA. When an ART entry of an historical event is coincident within a specified timeframe with a matched VA-prescribed medication, the likelihood is high that the ADR should be classified as observed rather than historical. Although this

Table 3.
Events Entered Into Adverse Reaction Tracking (ART) Database and Veterans Affairs (VA) Adverse Drug Event Reporting System (VA ADERS) and Submitted to FDA MedWatch[a]

Period	Entered Into ART	Entered Into VA ADERS	Submitted to FDA MedWatch
Fiscal year 2008			
Quarter 2	180,543	10,123	1,072
Quarter 3	187,014	11,054	1,167
Quarter 4	174,478	10,585	1,042
Fiscal year 2009			
Quarter 1	170,438	13,115	1,292
Quarter 2	190,061	15,526	1,238
Quarter 3	189,052	15,944	1,062
Quarter 4	196,409	15,455	953
Fiscal year 2010			
Quarter 1	186,588	16,292	1,001
Quarter 2	192,979	16,456	1,047

[a]FDA = Food and Drug Administration.

type of misclassification does not affect the ability of the system to trigger order checks, it does affect reports that are sent onward to the VA ADERS and, in some cases, to the FDA MedWatch program; this would be the case with any missed serious ADRs and ADRs associated with the use of newer drugs. The capability to track this type of misclassification error is now automated but is not yet universally used across the VA system; rather, it is available on request by individual facilities.

Case-finding and benchmarking. Apart from improving local processes, an important role for a comprehensive national database of adverse reactions is the application of monitoring and tracking methods across populations. These types of analyses—for example, assessing and verifying known ADRs and case-finding of rare events—remain very relevant to VA and the U.S. health care system. Furthermore, these analyses can supplement other forms of medication safety surveillance. For instance, if one method of pharmacovigilance (e.g., drug- and diagnoses-linked databases for the assessment of potentially new adverse outcomes) finds a trigger for a new drug with an estimated rate of 5 per 10,000 prescriptions and the voluntary (reporting) database yields information of an approximate rate of 2 per 10,000 prescriptions, it suggests that there may be a gap in clinician recognition of the adverse reaction or in reporting up the chain to the spontaneous-reporting database. A gap in understanding or reporting at the clinician level might then be addressed through educational efforts using specific feedback at the institution level.

The VA packages for ADR reporting have important limitations in addition to the previously mentioned potential for confusion in the designation of ADRs as historical or observed in the electronic medical record. Despite various educational efforts, including the use of a "hover hint" (cued onscreen text) that appears when choosing between the two classifications during ART data entry, anecdotal reports suggest that some clinicians are reluctant to enter an ADR as observed unless they personally see the reaction. This apprehension and misclassification can then result in an ADR not being documented with appropriate clinical information and reduce the likelihood that it will be reported to the VA ADERS or FDA.

Another limitation is that ADRs from within VA generally reflect patterns of utilization of drugs used frequently across the veteran population and may not reflect national drug-utilization and ADR patterns outside the VA system. For example, rates of serious mental illnesses are higher in the VA population than in the general U.S. population; thus, rates of atypical antipsychotic use are substantially higher among VA patients than in some other U.S. populations.[14] Therefore, ADR rates associated with the use of certain drugs within the VA system cannot be generalized to other health care systems.

Conclusion

In recent years, the refinement of two databases for ADR reporting has increased VA's capability to systematically monitor, track, and report ADRs across its national network of health care facilities. Linking the two databases has further strengthened those capabilities, enhancing medication safety practices and aiding in pharmacovigilance.

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