Adverse Drug Reaction Surveillance in Hospital Settings

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The World Health Organization (WHO) defines an Adverse Drug Reaction (ADR) as "any response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function."[1] An ADR is not to be confused with an Adverse Drug Event (ADE), which is a incident that may be preventable and that could be an ADR or a medication error. ADRs are unintended, adverse reactions that require pharmacovigilance (PV). Pharmacovigilance is a science incorporating the detection, assessment, understanding, and prevention of adverse effects, particularly long-term, and short-term side effects of medicines.[2]

Today's polypharmacy issues are a result from multiple disease states, food-drug interactions, drug-drug interactions, drug-herbal interactions, and new medications. There are now more concerns than ever about ADRs, effects on patients, and the cascade effect on the healthcare system at large. In fact, ADRs are the fourth leading cause of death — ahead of pulmonary disease, AIDS, pneumonia, accidents, and motor vehicle deaths.[3]

The incidence of ADRs has reached public awareness and has become a grave health concern that has increased over the last two decades. 89,842 ADRs were reported to the U.S. FDA in 2005, which is a 160% increase from the number reported in 1998. The rate of fatal ADRs increased even more significantly during the same seven years.[4]

While the overall incidence of ADRs is unknown, there are a number of known results of ADRs. Specifically, eight percent of Emergency Department visits result from ADRs; three to eight percent of hospitalized patients were admitted due to an ADR; approximately seven out of every 100 hospitalized patients will experience a serious ADR during the course of their stay; and about three of every 1,000 hospitalized patients will die resulting from an ADR.[5] Although not all ADRs are the result of medication allergies, the risk of an allergic reaction can occur up to 3% for most drugs, and one in 20 adults in the U.S. are allergic to at least one medication. The annual number of ADRs in ambulatory patients is not known, although skilled nursing facilities report 350,000 ADRs annually. Overall, 100,000 deaths from ADRs occur and over two million serious ADRs are experienced annually.[6]

The etiology of ADRs is in itself a science. The intrinsic factors of the drug may be pharmacologic, idiosyncratic, carcinogenic/mutagenic, or teratogenic. Extrinsic factors could include inactive ingredients, adulterants, or contaminants. In addition, a patient's underlying conditions, any known or unknown interactions, or even incorrect usage, and conditions for an ADR may present. Attention must be paid to whether an ADR, an ADE, or a basic medication error has occurred, and gathering precise information about the event is the key to proper surveillance and subsequent reporting.

Information on ADRs is obtained by a variety of methods. Clinical trials and animal experiments are critical. However, epidemiological methods present a great variety of data. These include observational studies (case reports and case series); post-marketing surveillance; cohort studies (via intensive hospital monitoring); case-controlled studies; and meta-analyses.

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1 Safety of Medicines: A Guide to Detecting and Reporting Adverse Drug Reactions. Geneva, Switzerland, World Health Organization, 2002. Available at: http://whqlibdoc.who.int/hq/2002/WHO_EDM_QSM_2002.2.pdf.

2 Pharmacovigilance: ensuring the safe use of medicine. WHO Policy Perspectives on Medicines. World Health Organization 2004. pp 1–5. Available at: http://whqlibdoc.who.int/hq/2004/WHO_EDM_2004.8.pdf.

3, 5 Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*, 1998; 279:1200–1205.

4 Arch Internal Medicine. 2010; 170:1142-1148, 1148-1149.

6 IOM National Academy Press 2000, Lazarou J et al. *JAMA*, 1998; 279 (15): 1200-1205. *American Journal of Medicine*, August 1, 2000; 109 (2): 122-30.

The role of the health care professional in capturing, assessing, and reporting ADRs presents specific challenges. If an ADR did in fact occur, the specific type of ADR must be determined. Root-cause analysis must be performed to differentiate human (provider) error from patient allergy from drug-drug interaction from pharmacokinetic profile. Polypharmacy must be assessed. Potential misdiagnosis of an exacerbated existing medical problem must also be ruled out.

CAPTURING ADRS

The patient is assessed for specific risk factors such as age, illness, sex, comorbid features, and concomitant illnesses.

The drugs are reviewed for proper dosage, duration, known toxicity, interactions, and timing.

The event is monitored for chart reports, onset of illness, disease exacerbation, and any new symptoms.

ANALYZING ADRS

The ADR Algorithm, specifically designed to analyze all relevant elements of an ADR, is an especially useful tool. The Naranjo algorithm Test for internal validity is easy to use, has great validity, and has a probability scale that is consensual in content.[7]

Table 1. The Naranjo Scale

To assess the adverse drug reaction, please answer the following and give pertinent score.				
Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	

REPORTING ADRS

On a regular basis, the pharmacy provides detailed reports to Medical Staff, Food and Drug Administration, Risk Management, Nursing, State agencies, and accrediting bodies.

Two types of reports are generated at GAMC to capture ADRs. The combination of the two provides double the avenues of reporting and increased awareness and participation.

Spontaneous reporting is completed by any and all licensed staff who have seen a medication error and wish to report. These reporters include nursing staff, pharmacy staff, medical staff, allied health staff, patients, and patient advocates.

The benefits of this method include the large population of reporters and the high volume of reports. The disadvantages include possible underreporting and potential bias.

Automated reporting is generated via a number of separate mechanisms. Daily reports include billing e-codes, reversal agent reports, IHI Trigger Tool reports, Automated Dispensing Unit reports that cite any and all medication dispensing, and other third-party vendor reports that measure medication orders, microbiology, and chemistry.

The benefits of automated reporting include unbiased reporting and the resulting increased awareness.

COST OF ADRS

ADRs are becoming an increasingly significant threat to the patient population, with the cost of ADRs estimated to be $1.5 to $4 billion per year.[8] One prospective study sought to compare hospital length of stay to total hospital costs in patients experiencing ADRs. A total of 247 ADRs occurred in 204 patients. Of the ADRs, 57% were considered significant; 30% serious; 12% life threatening; and 1% fatal. The drugs that caused greatest number of

7 Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clinical Pharmacology Therapy*, 1981; 30:239–245.

8 Reidl MA, Casillas AM. Adverse drug reactions: types and treatment options [Review]. *American Family Physician*, 2003;68:1781-1790.

preventable ADRs were analgesics, at 29%, followed by sedatives (10%), and antipsychotics (7%). The nonpreventable ADRs were caused by analgesics (30%), antibiotics (30%), oncologic agents (8%), and sedatives (7%). Allergic complications occurred in 7% of the patients and cardiovascular complications occurred in 16%.[9] Moreover, estimated preventable ADR costs are in the billions of dollars.[10]

Regardless of whether an institution utilizes spontaneous or automated ADR reporting, the continued monitoring and reporting of ADRs in the hospital setting is required to keep patients safe, maintain costs, and reduce errors. Pharmacologically, maintaining narrow therapeutic drug monitoring windows, maintaining an awareness of polypharmacy in mental health patients, and remaining vigilant with the elderly (using Beer's Criteria) all can help prevent ADRs. Awareness of patients at risk for falls, requiring that orders for anti-hypertensive include parameters as well as being alert for orders for multiple medications for the same indication without guidance on how and when to administer them also help prevent ADRs.

Accurate medication reconciliation, up to date medication references, and an engaged physician/pharmacy team can all be utilized to prevent ADRs, keep patients safe, and keep costs down. The key to preventing adverse drug reactions is staff ownership and pharmacy oversight. When the pharmacy works to manage patients proactively rather than reactively, and when physicians and nurses work as a team with pharmacy to keep patients safe, every hospital will be a safer place for every patient.

9 *JAMA* 1997; 277:304-311.
10 *JAMA* 1997; 277:304-311.