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# Why Don't We Adequately Identify and Manage Adverse Drug Reactions despite Having the Needed Information?

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## Abstract

**Importance/Objective:** Adverse Drug Reactions (ADRs) are unavoidable, but recognizing and addressing ADRs early can improve wellness and prevent permanent injury. We suggest that available medical information and digital/electronic methods could be used to manage this major healthcare problem for individual patients in real time. **Methods:** We searched the available digital applications and three literature databases using the medical subject heading terms, adverse drug reaction reporting systems or management, filtered by clinical trial or systemic reviews, to detect publications with data about ADR identification and management approaches. We reviewed the reports that had abstract or summary data or proposed or implemented methods or systems with potential to identify or manage ADRs in clinical settings. **Results:** The vast majority of the 481 reports used retrospectively collected data for groups of patients or were limited to surveying one population group or class of medication. The reports showed potential and definite associations of ADRs for specific drugs and problems, mostly, but not exclusively, for patients in hospitals and nursing homes. No reports described complete methods to collect comprehensive data on ADRs for individual patients in a healthcare system. The digital applications have ADR information, but all are too cumbersome or incomplete for use in active clinical settings. Several studies suggested that providing information about potential ADRs to clinicians can reduce these problems. **Conclusion and Relevance:** Although investigators and government agencies agree with the need, there is no comprehensive ADR management program in current use. Informing the patient's healthcare practitioners of potential ADRs at the point of service has the potential for reduction of these complications, which should improve healthcare and reduce unneeded costs.

**Keywords**

Adverse Drug Reaction, Medication Side Effect Identification, Medication Complication, Medication Safety

## 1. Introduction

An Adverse Drug Reaction (ADR) is "a response to a drug, which is noxious and unintended, and which occurs at dosages normally used for prophylaxis, diagnosis, or therapy of human disease or for the modification of physiologic function" [1]. ADRs represent a large component of the global problem of drug-related adverse events, and they have a huge negative impact on patient well-being, healthcare resources, and healthcare spending (approximately $30 billion per year in the United States [USA]) [2]. In emergency departments in the USA, ADRs are the cause of misdiagnoses and add a significant burden to the healthcare system [3]. Most investigations of ADRs are primarily in hospital settings. There are few reports from outpatient clinics, medical offices or nursing homes. This evidence suggests that the economic and healthcare impact of ADRs may be underestimated. While systems to address this issue are frequently recommended, few have been tested and none are widely available or implemented.

ADRs are just one of many pressures facing healthcare organizations, which include cost control while efficiently evaluating patients and providing high-quality care. These two goals seemingly conflict and are challenging as patients, particularly in the USA, are increasingly taking multiple drugs from a rapidly expanding list of medications. Many new agents, such as the "biologics" used to treat cancer and autoimmune disorders, have far-reaching effects that are often not fully understood when commercial use is initiated. Almost every drug can cause some degree of dysfunction or frank toxicity in one or more organ systems, which leads to symptomatic side effects. ADRs, particularly when not common, are frequently not considered or are unrecognized in the clinical setting; hence, these iatrogenic complications often worsen and can become severe. Recognized ADRs account for approximately 6.5% of hospitalizations [4] [5]. One report of 30,000 hospital records in the state of New York showed these complications can be irreversible, and lead to serious (6.7%) and fatal (0.32%) injuries, 13.6% of which appeared to be preventable [6]. At least 28% of hospitalizations due to ADRs seem to be preventable [7]. The elderly are at higher risk [8] [9] [10], perhaps related to multiple medication use. It is likely that the actual scope of the ADR problem is greater than estimated in reports, because most studies investigated a limited number of drugs, or reported drugs with a high frequency of moderate to severe ADRs, or ADRs were defined only by laboratory abnormalities, or only considered high-risk patients [11]. The frequency of ADRs in hospitals remains high [12] [13] [14] [15], and has not been reduced over the last 15 years, despite attention to the problem [16].

Although Adverse Drug Effects (ADEs) can also result from drug-drug interactions and prescribing contra-indications, these problems should be identified and managed at the time of prescribing by systems already created to identify these issues, prior to their occurrence. As there are adequate programs in place addressing drug-drug interactions, this report will not consider these issues. One review for primary care healthcare providers suggested that many ADRs are due to errors in prescribing and this could be potentially improved via medication safety programs [17]. As this should be implemented before an ADR occurs, we did not review the various medication safety programs designed to stop or prevent prescribing errors. We describe the status of healthcare addressing the specific problem of ADRs, many of which remain unrecognized and therefore are not addressed until too late, if at all. We focused on potential efficient approaches that are or could be used to identify ADRs to expedite management.

## 2. Methods

We performed a search of Cochrane Systemic Reviews from 1991 to 2023, PubMed, from January 1, 1984 to April 30, 2023, and JBI Database of Systematic Reviews and Implementation Reports from 2001 to December 31, 2023 using the medical subject heading term, adverse drug reaction reporting systems or management, filtered by clinical trial, meta-analysis, randomized control trial, and systemic reviews for humans. We reviewed the abstract or summary of each report to determine if each contained data about the extent of the ADR problem and proposed approaches to management. Subsequently, we reviewed all the articles of interest and highlighted and critiqued the reports with data in order to address the question: Are there proposed or implemented methods or systems that have potential to reduce adverse drug reactions in hospitals, clinics, or nursing homes? We also reviewed nine digital applications available to clinicians for accessing potential ADR information. We extracted the key elements of each study or application with focus on potential use within healthcare provider workflow.

## 3. Review of Findings and Analysis

### 3.1. Literature Review

We identified 278 publications in PubMed with data about the extent of the ADR problem and proposed approaches to management. Most studies and reports described retrospectively collected data, and were limited to specific populations and specific groups of drugs. The analysis below includes the reports that met our criteria for highlighting. Cochrane Systemic Review of ADRs identified 192 reports, none of which contained data about systematic identification or managing ADRs due to available medications. JBI Database of Systematic Reviews and Implementation Reports about adverse drug reactions from 2001 to December 31, 2023 showed 11 references and a single reference which focused on errors in prescribing [17].

One strategy used natural language to create an adverse drug effect recognizer

that uses admission electronic medical record medications, findings and past medical diagnoses to compare to a list of known ADRs. The system automatically notifies clinicians to existence of potential ADRs when a patient is hospitalized [18]. In a three-month study, the system extracted problems from the chief complaint, history of present illness, past medical history, medications and family history at pre-admission evaluations. The identified problems were then used to alert clinicians of potential ADRs, with a specific focus on antihypertensive adverse effects. For the clinicians that viewed the alerts, medication was reduced or stopped in 25% while a control group took the same action in only 15% ($p = 0.003$). At discharge, the medication was held or discontinued in 38% versus 23% in the control group ($p < 0.001$). This study showed that clinicians who are informed of potential ADRs will modify behavior and improve management. Unfortunately, this system did not include all potential ADRs for all medications [19].

Most of the published studies concern the frequency or prevalence of ADRs, almost exclusively after the events. Various methods report the association of ADRs and specific drugs or drugs with specific use indications, mostly in hospitalized patients. Recent work using bioinformatics shows the utility of using existing terms for identifying medical problems [Medical Dictionary for Regulatory Activities (MedDRAs)] to correlate with FDA blackbox warnings and labels [20] [21] [22], but this has not been done in real-time for active patient management. Computer systems can be utilized to reduce drug ordering errors and complications [23]. An integrated plan to prevent ADRs was proposed in 2014 but not implemented [24]. Additionally, the Centers for Medicare and Medicaid Services lists the various programs to reduce adverse drug events, none of which have been widely applied [25].

A trigger tool using laboratory tests to flag possible select ADRs, by association with abnormal laboratory values, revealed 40% of 162 individuals in USA Veterans Affairs nursing homes had potential ADRs [26]. Though each search takes only minutes per patient to accomplish, this method of ADR identification is based solely on laboratory data abnormalities. It is not comprehensive for all drugs and ADRs, as not all side effects are detectable with routine blood tests.

An 18-month study using a computerized system, comprised of pre-determined features of potential ADRs associations, provided daily reports to clinicians for hospitalized patients. Of 36,653 hospitalized patients, there were 731 (in 631 patients) moderate to severe ADRs found using a daily targeted surveillance of medical record data. The prescribing clinician was notified once an ADR was verified. The study recorded discontinuation of the provocative drug, but it did not report all management efforts or outcome for the identified ADRs. Although, the system was able to identify some ADRs, the number of unrecognized ADRs was probably considerably higher due to the limitation using pre-determined search parameters [27].

Another investigation, which used a combination strategy, composed of an expanded diagnostic code and e-prescribing data, found an increased detection

of ADRs in a study limited to two categories of drugs, agents for hypertension and depression [28].

The screening tool of older persons prescriptions and screening tool to alert right treatment methods, designed to highlight inappropriate medications in this demographic was applied once as an intervention within 48 hours of hospitalization in 360 of 732 patients 65 years of age or older. The physicians managing the care of the patients in the intervention group were notified of potential for ADRs. At least one ADR was noted in 11.7% of patients in the intervention group and in 21% of 372 patients whose healthcare provider was not informed. Medication costs were lower in the group with intervention [29]. This study showed that notifying physicians of the possibility of an ADR is a reasonable approach to reducing the problem.

### 3.2. Digital Databases for Clinicians

Nine applications for healthcare providers provide information about ADRs. Some are sponsored by the pharmaceutical manufacturers and most are typically searched by one drug at a time, e.g. using the drug package insert to provide a list of drug side effects [30]. One program provides a number of databases for drug and pharmaceutical information, including toxicology and drug interactions, but no specific database for adverse drug effects [31]. Another platform provides literature and focuses on pregnancy, lactation, toxicology, and laboratory tests, but not on ADRs [32]. Another platform emphasizes drug selection and drug interactions with drugs grouped by medical specialty, but not by ADRs [33]. There are other online comprehensive medical reference platforms that provide information on many aspects of drug use that can be searched for each drug. Prescribing guidelines are provided but the searches and data are not organized by patient-centric medical problems [34] [35]. Another comprehensive source is based on articles provided by the publisher periodically for author peer review. The authors use these articles to stipulate graded recommendations for clinical care decisions [36]. Searches are performed for individual drugs and the results are dependent on the metrics used by the authors and the timeliness of the data supplied by the publisher for each medical topic.

The FDA provides several sites to explore drug problems, all organized by a single drug (active ingredient or combination of ingredients and/or brand name). The first two sites require searching each document for reported adverse drug events to determine the frequency in each study performed for the drug approval process. Drugs@FDA contains medical and other reviews that have ADRs included, and are typically found under new drug approvals (https://www.accessdata.fda.gov/scripts/cder/daf/). Dailymed contains most of the FDA labels, which contain ADR information that should be similar to the medical review data [37]. The FDA adverse event reporting system contains reports for drug side effects, but they are unverified, may have duplicate reporting and there is no way to determine the frequency or prevalence of the side

effects [38].

## 4. Discussion

We could not find a comprehensive tool to identify ADRs that can be used efficiently, whether it is in a clinic, hospital, emergency department, nursing home, pharmacy or telehealth setting. Each available approach can be helpful, but all are of limited use due to complexity of utilization, the amount of time and effort (that interferes with clinical workflow), or incomplete (e.g. out of date) content. Thus, clinicians often remain unaware of many ADRs, continue medications that harm patients, or add medications in a prescribing cascade [39] [40] [41] [42] [43]. Without a process to identify ADRs that fit into clinician workflow, no plan to foster de-prescribing will be successful [44]. A National Action Plan for Adverse Drug Event Prevention, published in 2018, targeted just three types of therapies, anticoagulants, diabetes agents, and opioids [45]. The plan recommended surveillance, prevention, incentives, oversight and research, with federal agencies coordinating and collaborating with public and private sectors. This was followed by funding announcement to address medication safety strategies and tools by the USA Agency for Healthcare Research and Quality in 2019 [46]. Most of the grantees focused on anticoagulation, opioids, and anti-depressant medications [47]. Studies that address a specific group of "high impact" therapeutics have been published, but no global plan or tool to identify unrecognized ADRs has resulted.

There are almost no articles describing efficient potential solutions that can be implemented in clinical practice to reduce ADRs [18]. New prospective data are now being collected and will likely demonstrate that the problem is more widespread [48], but this is not a substitute for identifying ADRs in real-time and developing processes for ADR reduction. Many articles and reports describe the huge negative impact of ADRs, particularly on hospitalized patients and individuals in long-term care/nursing home facilities, where data is more available. Many ADRs are actually present on admission and often continue while a patient is in the hospital [49]. It appears that the most at-risk individuals are the elderly, dementia patients, and those with chronic illnesses. The actual scale of the problem will be considerably greater once data from outpatient/clinic settings are considered [48] [50]. One report stated that only 5% of ADRs were recognized [51]. We also suspect that federal discussions about requiring mandatory ADR reporting by healthcare providers are tempered by the realization that ADR identification is limited.

Although many ADRs are noted during premarket clinical trials and described and listed in the medical reviews on the drugs@FDA site, many ADRs are discovered post-marketing and reported in published articles. Additionally, some randomized clinical trials do not always accurately report the frequency or severity of ADRs [52]. Thus, it is imperative to consider all potentially available data, including post-marketing monitoring as drug safety information evolves over

months and years after approval [53] [54]. Despite these efforts, major challenges remain to the voluntary reporting programs, leading to deficiencies that result in difficulties in diagnosing and reporting ADRs [55].

Healthcare system and practice decision-makers should prioritize reducing ADRs. This would immediately improve the value of healthcare, besides limiting injury and deaths. Healthcare organizations and systems that have capitated contracts or are "closed systems" would immediately have measurable return on investment. Closed healthcare systems, like the USA Veterans Health Administration (VHA) clinics, hospitals and nursing homes, should be the optimal institutions to demonstrate the benefit of the needed system and should have effective reporting capability. For example, a VA registration system, based on a web-based system to identify ADRs, collected approximately 60,000 reports across the 146 outpatient facilities over a seven-year period [56]. As of May 2020, the VHA reported a directive "for the reporting, monitoring, and surveillance of Adverse Drug Events (ADEs) entered into VHA's voluntary ADE reporting system for observed Adverse Drug Reactions (ADRs) and new ADEs at Department of Veterans Affairs (VA) medical facilities" [57]. After the many reports describing the huge negative impact on the health of the population of the USA, including Veterans, there is virtually no system in place to improve safety by identifying and reducing ADRs in the VHA system.

The least intrusive and lowest cost process appears to be an approach that informs the healthcare providers and prescribers of prescription drugs within their workflow [13] [18] [27] [29]. Focusing on physicians, nurses, physician assistants, and pharmacists should be an effective strategy. As no clinician can be aware of all potential ADRs, healthcare providers require complete data-driven information [58] [59]. The clinician will always be needed to determine the causality for each potential ADR once the possibility is presented [60]. The report by Smith *et al.*, which notified physicians of potential ADRs, showed under 50% utilization by doctors with just an early pilot effort [18]. Furnishing healthcare professionals with a proper tool that provides comprehensive quality data is required. Using databases like the Systematized Nomenclature of Medicine (SNOMED) and MedDRA preferred terms to organize drug side effects from FDA labels in the strategy has already been described [60]. In the future, deep learning methods should assist the clinician with evaluating an individual patient's likelihood of having an ADR. Deep learning of electronic health records and other data sources will increase the capabilities to apply all these data. However, the medical records must be accurate, with complete assessments of symptoms, problems, laboratory test results, and all medications to identify potential temporally associated ADRs and possibly predict ADRs from similar new compounds. The creation of a deep learning tool will require vast amount of carefully synthesized data for all drugs and side effects before it can be utilized in clinical situations [61] [62].

Unfortunately, the current platforms and applications available for clinician searches for drug side effects are not patient-problem-centric. The information

platforms available to healthcare providers are not always current, do not rank content by the level of evidence, do not reflect the latest medical literature, do not provide enough information on medications and reported side effects, and are unwieldy and inefficient, they are not routinely utilized in a clinical setting. We are faced with a remarkable inefficiency, where large amounts of publicly available information cannot be accessed in an economical fashion by clinicians. We suggest that providing a platform that addresses the issues at the point of service should effectively change the healthcare culture. ADRs will be routinely considered, which will lead to improved management. We consider this approach the digital equivalent of "hand washing to reduce infection spread" as a method to lessen iatrogenic illness. Patient expectations will be elevated, and use of evidence-based decision-making to identify and reduce ADRs will become an important metric of clinician performance. We should not wait for all-encompassing safety programs to be developed that require significant management by administrators or pharmacists. ADRs are a major healthcare problem that is addressable at fraction of a cost required to create new procedures or drugs. Perhaps, healthcare groups and systems will only take this seriously and implement methods to identify and reduce ADRs when payers and the government require this as part of safety and quality parameters.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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