

Adverse Drug Reactions and Inappropriate Prescribing: An Overview

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Introduction

Early human society believed that disease states resulted from sorcery, demonic possession, negative astral influences, and “the will of the gods” [17]. No record exists establishing the date when plants were first used for medicinal purposes, but it is known that herbalism was practiced in the prehistoric world. Modern medicine began in the 19th century with revolutionary advances in the fields of synthetic chemistry, laboratory science and technology, and microbiology. Though plant-derived compounds such as morphine, quinine, and digitalis were widely used prior to that time, the first modern synthetic chemotherapeutic agent was not discovered until 1908, when a research team headed by Paul Ehrlich described the anti-syphilitic properties of arsphenamine [15]. In 1910, the compound was marketed as Salversan 606, as it was the 606th compound synthesized for testing by Ehrlich’s team [16]. Thus, the modern age of pharmacotherapy began.

Since the discovery of Salversan 606, the pharmaceutical industry has exploded into a multi-billion dollar global industry. Legislation has been enacted to regulate the development, marketing, and distribution of pharmaceutical agents. The distinction between prescription and non-prescription drugs grew out of this legislation. The term *prescription drug* refers to those medicines that can only be distributed by the order of a qualified medical professional. In the United States, dispensation of prescription drugs can be authorized by a variety of medical professionals, including physicians, physician assistants, nurse practitioners, dentists, and veterinarians. Prescription drugs are regulated in the United States by the Food and Drug Administration (FDA), under the authority a number legislative initiatives and amendments codified in Title 21, Chapter 9 of the United States Code. Specifically, prescription drug safety and efficacy regulations are enumerated in the Prescription Drug Marketing Act of 1987. [18]

In the 1960s, in the wake of the thalidomide tragedy, a number of prospective trials were undertaken in an effort to quantify the incidence of significant adverse drug reactions (ADR) in hospitalized patients [2,7]. These prospective studies generally addressed two separate patient populations: (1) those admitted to the hospital as a result of an ADR and; (2) those who suffered an ADR while hospitalized for some other reason. In a reviewing 39 of 153 of these prospective studies performed between 1966 and 1996, Lazarou et al found an incidence of serious ADRs of 4.7% and 2.1% and an incidence of fatal ADRs of 0.13% and 0.19%, respectively, in the two population groups. [7]

Statistical analysis, by Lazarou et al, of fatalities among hospitalized patients in the United States during 1994 revealed that approximately 106,000 deaths (95% confidence interval, 76,000 - 137,000) could be attributed to adverse drug reactions. According to this study, even at the lower confidence limit of 76,000 deaths, adverse drugs reactions would have ranked as the sixth leading cause of death among inpatients that year—

behind cardiovascular disease, cancer, stroke, pulmonary disease, and accidental trauma. [7] This analysis would not have included fatalities resulting from adverse drug reactions occurring outside the hospital setting and, thus, may have underestimated the number of deaths attributable to adverse drug reactions in that year.

These findings underscore the potential significance of adverse drug reactions in the broader population. This population is comprised, essentially, of most citizens of countries in the developed world. Considering the United States alone, with a population of roughly 300 million, adverse drug reactions have a huge public health impact in terms of mortality, morbidity, and resource cost. Consequently, issues of inappropriate prescribing on the part of health care professionals and inappropriate access to prescription drugs through black and grey market sales, both of which are likely to increase the incidence of adverse drug events, represent a significant public health concern, as well.

Adverse Drug Reactions

An *adverse drug reaction* (ADR) is defined, for epidemiological purposes, as “any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis, or therapy. This definition excludes therapeutic failures, intentional and accidental poisoning (i.e., overdose), and drug abuse.” [7,19] Additionally, the definition excludes adverse events related to errors in drug administration or non-compliance [19].

Fatal ADRs: A Representative Study

In a 2007 study by Wester et al, the medical records of 1574 deceased study subjects were reviewed to determine the number of deaths related to adverse drug reactions. 49 patients were suspected to have died from an ADR (3.1% of the study population, 95% CI 2.2% - 4.0%). Hemorrhagic events were, by far, the most common fatal adverse drug reactions. Gastrointestinal hemorrhage occurred in 18 (37%) patients and central nervous system hemorrhage was noted in 14 (29%) patients. There were 6 other fatal hemorrhagic events—*intra-abdominal* (2, 4%), *bladder* (1, 2%), and *respiratory tract* (1, 2%). Cardiopulmonary events accounted for 5 (10%) fatal ADRs. The remaining fatalities were attributed to *renal dysfunction* (2, 4%), *cystitis* (1, 2%), *hyperkalemia* (2, 4%), *pseudomembranous colitis* (1, 2%), *agranulocytosis* (1, 2%), and *generalized seizures* (1, 2%). In the cases of fatal hemorrhage, the following drugs were implicated most often:

1. Antithrombotic agents (31/36, 86%), including acetylsalicylic acid (aspirin—20, 43%), warfarin (Coumadin®—8, 16%), dalteparin (low molecular weight heparin—7, 14%), and dipyridamole (Persantine®—4, 8%);
2. Selective serotonin reuptake inhibitors (SSRI antidepressants) (7/36, 19%), most notably citalopram (Celexa®—6, 12%) and;
3. Non-steroidal anti-inflammatory drugs (NSAIDs) (6/36, 17%), most notably celecoxib (Celebrex®—2, 4%), diclofenac (Voltaren®—2, 4%), naproxen (Naprosyn®—2, 4%), and rofecoxib (Vioxx®—2, 4%). [14]

ADR-Related Hospital Admissions: A Representative Study

A 2004 study by Pirmohamed et al prospectively evaluated 18,820 patient admissions to two large general hospitals in Merseyside, England over the course of a 6-month period to assess the “burden of adverse drug reactions” on the National Health Service (NHS) [11]. 1,225 (6.5%, 95% CI 6.2% - 6.9%) of the admissions were identified as having been related to an ADR, with 80% of those having resulted directly from the ADR. Adverse drug reactions accounted for a death rate 0.15% (28/18,820) among the study population and a death rate of 2.3% (28/1,225) among the ADR-related admission subgroup. Patients admitted with ADRs were significantly older (median age = 76) than those without ADRs (median age = 66) and the percentage of women comprising the ADR group was significantly higher (59%) than that of the non-ADR group (52%). Further statistical analysis of the ADR-related admissions suggested that only 340 (28%, CI 25% - 30%) of the ADRs were *unavoidable*. Thus, 72% of the ADRs were classified as potentially avoidable.

Gastrointestinal hemorrhage was the most common fatal ADR (15/28, 54%), while central nervous system hemorrhage and renal failure accounted for 5 (18%) deaths each. Non-steroidal anti-inflammatory drugs were the most commonly implicated class of drugs related to ADRs in this study (363/1,225, 29.6%) followed by diuretics (334/1,225, 27.3%) and warfarin (129/1,225, 10.5%). Acetylsalicylic acid was the most commonly identified individual drug related to study ADRs (218/1,225, 18%). Warfarin was next most commonly implicated. The median ADR-related hospital admission was eight days (4% of hospital bed capacity), yielding a projected annualized cost of such admissions across the whole of the NHS of approximately \$847 million. [11]

Inappropriate Prescribing

Age-related changes in physiology, body composition, and pharmacokinetics account for a portion of the increased risk for ADRs among the elderly (age 65 and greater). Older patients frequently have multiple medical conditions for which they may be taking several prescription medicines concurrently. These factors place the geriatric population at distinctly higher risk for clinically significant ADRs. [4]

Inappropriate prescribing is highly prevalent in the geriatric population, with approximately one-quarter of the community-dwelling elderly and nearly one-half of nursing home residents regularly receiving at least one potentially problematic prescription drug [2, 3, 5]. *Inappropriate prescribing* entails the use of medicines that pose more risk than benefit, the misuse of drugs by dose or duration, and the prescribing of medicines with known, clinically significant drug-drug and/or drug-disease interactions [2, 10]. Suboptimal or inappropriate prescribing is associated with increased mortality, morbidity, and resource cost, largely related to the prevalence of adverse drug events [2, 3, 5].

A 2005 study by Taylor et al, utilizing an electronic prescription and drug-disease management system, evaluated and categorized the spectrum of alerts arising from

inappropriate prescribing practices over a consecutive nine-month period in an urban community setting in Montreal, Quebec. During the study period, a total of 22,419 prescriptions generated 6,428 alerts (29% of total prescriptions). *Drug-disease contraindications* were the most prevalent source of alerts, accounting for 41% of the total. Of this category of error, the most common medication classes involved were antidepressants (n=376, 9%, primary contraindication of underlying cardiovascular disease), NSAIDs (n=192, 7%, primary contraindication of underlying asthma), and thyroid replacement therapy (n=122, 5%, near sole contraindication of underlying cardiovascular disease). *Drug-drug interactions* accounted for nearly 24% of total alerts. Of this category of error, the most common medication classes involved were β -blockers (n=81, 5%, primary contraindication of potentially negative interaction with antidepressant co-therapy), HMG-CoA Reductase Inhibitors (“statins”) (n=77, 5%, primary contraindication of potentially negative interaction with calcium channel blocker co-therapy), and NSAIDs (n=65, 4%, primary contraindication of potentially negative interaction with insulin or sulfonylurea co-therapy). *Potential toxicity* represented about 9% of total alerts. *Drug duplication* errors accounted for 5% of alerts. *Age-related contraindications* generated 0.5% of total alerts. Antidepressant co-therapy accounted for the primary contraindication in each of the latter three cases. [12]

Overprescribing

Overprescribing of some classes of prescription drugs is a significant public health issue. For instance, the prescription of antibiotics to patients with viral upper respiratory infections and the overuse of broad-spectrum antibiotics in the treatment of bacterial illness are prevalent and sub-optimal practices. Such inappropriate prescribing practices contribute to the genesis of antibiotic-resistant pathogens, an increased incidence of adverse drug events, and uncontrolled growth in the costs of health care services [1, 9].

A Canadian study by Cadieux et al, published in 2007, noted the following predictors of increased incidence of inappropriate prescription of antibiotics: (1) International medical education and graduation (as opposed to Canadian or U.S. education and graduation); (2) physicians with more time in clinical practice, relative to their peers, and; (3) physicians engaged in high-volume practices. Numerous studies suggest that other classes of drugs such as proton-pump inhibitors, antidepressants, and benzodiazepines are inappropriately overprescribed for a host of reasons.

Abuse of Prescription Drugs

Abuse of prescription drugs has increased steadily over the years. The 2005 National Survey on Drug Use and Health suggested that 6.4 million (2.6%) Americans, aged 12 or older, had used controlled psychotherapeutic drugs for non-medical purposes in the month prior to completing the survey. “Of these, 4.7 million used pain relievers, 1.8 million used tranquilizers, and 1.1 million used stimulants (including 512,000 using methamphetamines) [8]. Illicit black market sale of prescription drugs is a lucrative and well-established criminal enterprise. The rise of the Internet pharmacy has served to make prescription drugs and drugs of abuse, in particular, more readily available to the

public. These pharmacies often provide prescription drugs to patients with little or no documentation and frequently do so despite clear medical contraindications [13].

Summary

While any organ system can potentially be affected by an adverse drug reaction, the literature suggests that drug-induced hemorrhagic events, gastrointestinal and central nervous system hemorrhage, in particular, are the most commonly fatal ADRs. Cardiopulmonary events and renal failure appear to be the next most common causes of ADR-related fatalities. NSAIDs and antidepressants seem to be the most problematic classes of therapeutic agents, in terms of the overall incidence of ADRs, while antithrombotic agents and NSAIDs have been most commonly implicated in ADR-related deaths.

The public health significance of adverse drug reactions in terms of mortality, morbidity, and resource allocation is obvious. Roughly 5% of hospital admissions are related to adverse drug reactions, with an estimated cost of \$16,000 per admission [6]. Approximately 3% of patients with ADR-related hospital admissions die as a result of the ADR. Adverse drug reactions are responsible for a death rate of approximately 0.15% of all hospitalized patients. The cited studies suggest that a significant number of adverse drug reactions were related to inappropriate prescribing practices on the part of health care practitioners and were, therefore, likely to have been preventable.

These mortality and morbidity figures do not account for adverse events associated with the non-medical use of prescription drugs obtained through black market dealers or via Internet pharmacies. However, the inappropriate use of prescription medication by the public at-large is dangerous and can only add to the incidence of costly adverse drug reactions. Clearly, the optimization of prescription drug use and minimization of related adverse effects are important public health issues that warrant further study.

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