Adverse Drug Events: Causes, Costs, and New Directions For Prevention

By Sandra Leal, PharmD, MPH

Adverse drug events (ADEs) defined

Prescription and over-the-counter medications are essential to the health and well-being of millions of people in the United States. Yet these very same life-changing, sometimes life-saving medications can also cause serious harm to the patients they are meant to help.

Misuse of medications, whether intentional or not, can result in serious harm. Even when used as directed by a prescriber, medications can cause unexpected reactions and side effects that compromise the health of the patient.

"Adverse drug event" is the catch-all term used to describe medication-related harm, including harm coming from appropriate use of the medication(s) in question.[1]

Harm that results from use of a drug in accordance with accepted medical practice is known as an adverse drug reaction (ADR).

ADRs — including anaphylaxis and drug-drug interactions — are sometimes described as non-preventable ADEs.

Classification of Adverse Drug Events

ADE is a catch-all term that includes Adverse Drug Reactions (ADRs). Drug-drug interactions (DDI) are a clinically important sub-set of ADRs.

This publication presents evidence of the massive clinical and financial toll imposed by ADRs, in order to raise awareness and spur the development of innovations to prevent ADRs. I hope that, in the near future, the science of patient safety will advance to the point where we will no longer view any ADE as non-preventable.

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The cost of "non-preventable" ADEs

Taken as a whole, ADEs are responsible for one third of all hospital adverse events in the inpatient setting. An ADE also increases the length of a patient's stay.[2] And, with an estimated 1 million emergency department (ED) visits and 125,000 admissions annually from ADEs, they are clearly taking a toll in the outpatient setting as well.[2]

Drug-drug interactions (DDIs)

If we narrow the focus to ADRs alone, their impact on patient safety is startling, with more than 2 million events occurring annually in the US.[3] Interactions between drugs (DDIs), a common category of ADRs in the US, account for up to 20% of all adverse drug events.[4] Estimates of the financial impact, considering healthcare expenditures alone, of drug-drug interactions range from $30 to $180 billion.[4]

The ever-expanding U.S. pharmacopeia complicates matters, as some relatively rare events, including interactions with other medications or foods, may not emerge until after a new drug is approved. The available data bear this out, with the majority of clinically significant drug-drug interactions going unrecognized and untreated by primary care providers.[4]

Who is at risk for drug-drug interactions?

Key risk factors for DDIs have been identified. Unsurprisingly, polypharmacy is an important risk factor for DDIs.[5] However, the steep rise in risk with increased number of prescriptions is worth mentioning: by one estimate, the risk of a DDI is 50% for a patient taking 5-9 prescriptions, rising to 100% for patients taking 20 prescription medications.[6]

DDI risk increases with higher number of prescriptions.[6]

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And the fact is, there are many patients in the US at any given time who are taking several prescriptions concomitantly. The average 65-year-old in the US takes four prescription medications, so polypharmacy is not a statistical outlier.[4]

Drugs with a narrow therapeutic index

Drugs in which small changes in blood concentration or dosage can lead to therapeutic failure or other adverse events are said to have a narrow therapeutic index (NTI). Warfarin is a classic example — too little anticoagulant activity and patients face an increased risk of stroke; too much and they are prone to bleeding events. NTI drugs pose particular challenges to patients and their care providers and appear to be associated with an increased risk for a DDI.[7]

Social determinants of health

Patients are people, not constellations of symptoms and signs. We have seen time and again that non-medical factors can have a huge impact on health. These social determinants of health include education, access to healthcare, and social and community standards and norms.

Specific social factors associated with an increased risk for ADEs include limited health literacy and low numeracy (i.e., the ability to use arithmetic in typical daily tasks).[8] These factors likely make it difficult for some patients to understand and follow complex multi-drug dosing regimens, increasing the chance of an ADE.

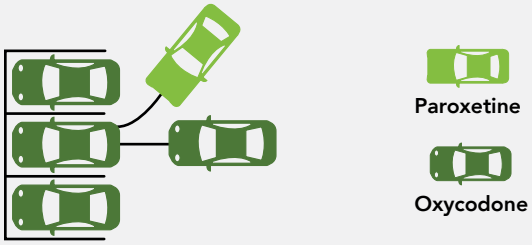
Can we prevent "non-preventable" ADEs?

At this point, the magnitude of the clinical and financial impact of ADEs is clear. In the broadest terms, morbidity and mortality associated with non-optimized medication regimens cost the US $528 billion in 2016.[9] This financial toll, staggering though it may be, is overshadowed by the human suffering associated with ADEs.

One of the first and most important steps in reducing adverse drug events and increasing patient safety is to improve the reporting of these events, which most researchers agree are substantially under-reported.[10] A variety of interventions are possible, with multifaceted strategies utilizing electronic tools showing particular promise.[11] Other publications have noted that EHR-based reporting solutions may be attractive solutions to increase clinicians' reporting of adverse drug events because they are integrated into a well-known and frequently used workflow.[12]

Assessing potential cumulative, synergistic, or antagonistic effects of multiple agents is another important avenue for additional research. As noted above, drug-drug interactions are a significant source of medication-related morbidity and mortality. With polypharmacy becoming the norm rather than an outlier among older patients, it is vital to move beyond the usual models of drug interactions that focus on interactions between two agents. While it is important to characterize and encourage reporting of one-to-one interactions, it is equally important to begin unraveling the complexities and interactions associated with multiple concomitant medications.

Competitive inhibition is responsible for some DDIs.



In this example, oxycodone and paroxetine compete for the same receptors, potentially altering the effects of one or both drugs.

An expanded understanding of such multi-drug interactions is vital for the improvement of drug safety. Quantification of these complex interactions will enable the development of solutions to reduce the risk of ADEs among patients who use several medications. Ideally, we will enter a new era of medication safety where multiple factors, including the patient's genetic profile and the complex interplay among multiple medications and the underlying conditions they are intended to treat, are balanced in order to achieve the best therapeutic result with the least risk to the patient. That kind of optimized therapeutic regimen will be a major step forward for patients, of course—but also an important way of containing medical costs for public and private payers.

Key takeaways:

ADEs exact a huge toll in terms of morbidity, mortality, and healthcare expenditures

Drug interactions are common among patients taking multiple medications

A better understanding of the mechanisms of multi-drug interactions will point the way to solutions that can prevent these ADEs

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Sandra Leal has published and presented her work in numerous national and international publications and venues including Peru, India, and Japan. She has been recognized as the Good Government Pharmacist of the Year by the American Pharmacists Association (APhA) for her advocacy work on pharmacist provider status. Dr. Leal is a two-time recipient of the Pinnacle Award from the APhA Foundation for her progressive practice innovations and received the ASHP Best Practice Award for her leading practice in diabetes management.

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