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Health Affairs 9, no.3 (1990):114-122
doi: 10.1377/hlthaff.9.3.114

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Commentary

Adverse Drug Reactions And The Elderly
by Wayne A. Ray, Marie R. Griffin, and Ronald I. Shorr

Virtually all medications can produce undesirable side effects. The elderly are more likely to experience these adverse reactions as the result of age-related increases in the frequency of drug use, sensitivity to drug effects, and prevalence of predisposing conditions that can increase the frequency and severity of adverse drug reactions.

Because the prevalence of disease increases with age, the elderly are frequent medication users. Persons age sixty-five or older comprise 12 percent of the U.S. population but use 32 percent of prescribed medications.\(^1\) The point-prevalence of prescription drug use is 80 percent for persons age sixty-five or older in the community, and even higher for those in nursing homes.\(^2\) The classes of medications used most commonly by the elderly include cardiovascular drugs, antimicrobials, analgesics, hypoglycemic agents, psychotropic drugs, and anti-arthritis.\(^3\)

Increased sensitivity to drug effects among the elderly results from changes in pharmacokinetics (how the body absorbs, transforms, and excretes medications) and pharmacodynamics (the effect of the drug on the body). For many drugs, both the half-life of and active levels produced by a given dose increase with age, and for some drugs, a given active drug level will have a greater effect in older persons.\(^4\) This increase in sensitivity results from age-related changes in gastrointestinal, hepatic, and renal function; body composition; and drug receptor dynamics. Age-related losses of physiologic function also may predispose the older patient to adverse drug reactions. For example, there is an average loss of approximately 0.5 to 1 percent of kidney filtering capacity each year after the fourth decade, so that a typical eighty-year-old has only 60–80

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percent of the renal function of a forty-year-old.\textsuperscript{5} This increases the susceptibility of the older drug user to drug-induced renal failure. Furthermore, the elderly are more vulnerable to both drug/disease and drug/drug interactions.

The increased risk of hip fracture among older users of sedative drugs is one example of how the interplay of increased likelihood of drug use, increased sensitivity to medication effects, and increased frailty enhances the risk of serious, life-threatening injury. Because the prevalence of insomnia rises with age, there is increased sedative use among the elderly.\textsuperscript{6} A common effect of sedatives is reduced coordination and alertness, which is intensified and prolonged in elderly patients.\textsuperscript{7} One consequence of this impairment is an increased risk of falling, which may be further magnified in older patients who have other problems that decrease postural stability.\textsuperscript{8} Finally, age-related loss of bone mass increases the risk that the elderly person who falls will sustain a fracture.

### The Knowledge Deficit

Given that at least twenty-six million persons age sixty-five or older use prescribed medications regularly, one would expect that the risk of adverse drug reactions and the attendant health care costs would be well quantified for this population. This is not the case, however. A widely cited figure is that in the population at large, medication toxicities cause between 3 percent and 5 percent of hospital admissions, resulting in costs of $3 billion annually.\textsuperscript{9} However, these studies have been restricted to easily recognized adverse drug reactions, such as a skin rash and fever that resolve when the drug is withdrawn, and thus would not include cases in which the causal link between drug and disease was not apparent or in which the drug increased the risk of a disease with other causes, such as a hip fracture in a patient receiving a sedative drug. Thus, it is likely that these figures understate the extent and consequences of the problem.

Epidemiologic studies are required to quantitate the increased risk of a disease that is attributable to a drug. These studies calculate the incidence of disease in persons receiving and not receiving the drug. The ratio of these two rates, adjusted for other factors associated with both drug and disease, estimates the increase in risk of disease incurred by drug users. For example, epidemiologic studies have found that elderly persons receiving psychotropic drugs have a 70–100 percent increase in the risk of hip fracture.\textsuperscript{10} To determine accurately the excess risk for major illness, studies that encompass populations with 10,000 to 1,000,000 persons are necessary.

One opportunity to quantitate this risk of adverse reactions occurs
before a new drug is licensed. Efficacy is established in carefully controlled clinical trials that generally encompass up to 1,000 patients receiving the new drug. However, this sample size is not large enough to determine the drug’s potential for adverse reaction. The capacity of premarketing studies to do so is further reduced by the limited number of patients age sixty-five or older in such trials and the even smaller numbers of the oldest old. Furthermore, the study duration is usually too short to detect effects of long latency, such as cancer. Finally, these studies often exclude persons with poor health or who are taking other medications, even though this group may be the most susceptible to adverse drug reactions.

Once a medication has been licensed, adverse drug reactions may be detected in postmarketing surveillance studies mandated by the Food and Drug Administration (FDA), case reports of adverse drug reactions, and ad hoc epidemiologic studies. For medications for which there is a specific concern (only a minority of new products), FDA may require postmarketing epidemiologic studies as a condition of licensing. In the United States, the primary source of case reports is FDA’s spontaneous reporting system. Pharmaceutical manufacturers are required, and physicians and other health care providers are encouraged, to promptly forward reports of adverse drug reactions to FDA. The other major source of case reports is the medical literature. The capacity to detect adverse drug reactions with case reports is limited by their reliance upon a physician (or other health care provider) to recognize cases, incomplete reporting, lack of a denominator, and difficulty in establishing a causal link between the drug and the disease. Thus, case reports are most valuable for identifying distinct clinical entities that occur with relatively high frequency soon after drug administration. These reports cannot establish causality when the background rate of disease is substantial (such as hip fracture or peptic ulcer disease in persons over age sixty-five) and thus are less useful in elderly populations.

Much of what is known concerning adverse drug reactions in the elderly comes from properly controlled epidemiologic studies. Examples of drug/disease associations elucidated with this method include medications and falls or fall-related injuries, nonsteroidal anti-inflammatory drugs (NSAIDs) and peptic ulcer disease, antipsychotics and movement disorders, and antidepressants and cardiovascular side effects. However, ad hoc epidemiologic studies of adverse drug reactions generally are conducted only after substantial questions concerning a drug’s safety have been raised. Because funding for these studies is quite limited, they often have methodologic deficiencies that preclude a definitive resolution and may serve only to generate controversy that ultimately leads to
better studies. This problem is magnified for studies of adverse drug reactions in elderly patients because research in this population is often more difficult and expensive.\textsuperscript{13}

The lack of systematic epidemiologic studies means that decades may elapse before the risks of a medication are quantified, even for drugs with potentially life-threatening toxicities that are used commonly by elderly patients. An excellent example is provided by NSAIDs, which are used primarily among the elderly for the treatment of arthritic symptoms. The best known NSAID, aspirin, has been available since 1899, and the first prescription NSAID, phenylbutazone, was licensed in 1946.\textsuperscript{14} The physiologic effects of NSAIDs, which may interfere with the stomach’s capacity to resist the corrosive effects of gastric acid, have led to the concern that they increase the risk of clinically significant peptic ulcer disease. Determining whether or not this occurs is of major public health importance: NSAIDs are used by 14–18 percent of persons over age sixty five on a given day (probably another 5–10 percent use over-the-counter NSAIDs), and peptic ulcer disease can have serious complications in elderly patients, including death in up to 8–12 percent of hospitalized cases.\textsuperscript{15} Most of the epidemiologic studies of this question have reported a threefold or more increased risk of ulcer disease among elderly NSAID users. However, until recently, many of these studies were of limited size and methodologic sophistication.\textsuperscript{16} Thus, controversy as to the magnitude of increased risk of ulcers among NSAID users has persisted for decades and continues to be active, even though an expensive drug is marketed specifically to prevent this adverse NSAID effect. Other unresolved questions concerning the safety of NSAIDs in elderly patients include their role in lower gastrointestinal tract disease, kidney failure, liver damage, interference with efficacy of antihypertensive medications, and acute delirium.

There are numerous other unanswered questions concerning the safety of drugs commonly used by the elderly. These include uncertainty as to whether a drug causes an adverse drug reaction, or, in those cases in which the causal link is accepted, uncertainty as to the magnitude of increased risk.

Even in the unusual circumstance in which the incidence of an adverse drug reaction is well quantified, its overall medical and economic impact may be uncertain because the number of elderly persons exposed to the drug is not known. That is because there are no accurate, ongoing estimates of the prevalence of drug use for representative patient populations. National data collected for marketing research do not use the person as the sampling unit and thus are not suitable for this purpose. There are numerous studies that ascertain the prevalence of use of certain
drugs within special populations; however, these noncomprehensive data rapidly become dated, and the populations studied may not be sufficiently representative to permit national extrapolation.

Medical And Economic Consequences

Despite our incomplete knowledge of the overall frequency of adverse drug effects among older persons, we know from specific examples that medication toxicities can have profound medical and economic consequences. These include an increased risk of serious disease, with potential long-term disability, institutionalization, and death; these in turn generate increased expenditures for medical care. The potential magnitude of these consequences can be illustrated by considering two examples: hip fracture and peptic ulcer disease.

In the United States, 217,000 persons age sixty-five and older sustained hip fractures in 1987. We found in a Medicaid population that as many as 14 percent of these fractures may be attributable to psychotropic drug use. If this estimate is correct and can be generalized to non-Medicaid elderly, then use of these drugs results in 30,000 excess hip fractures each year. Among these patients, there will be a 10–15 percent excess mortality rate in the year following the fracture, 50 percent will lose the capacity to walk independently, and up to one-third of those formerly dwelling in the community will require long-term nursing home care. The annual direct medical care cost associated with these 30,000 cases is approximately $1 billion.

Among persons age sixty-five or older, the rate of hospitalization for peptic ulcer disease was 4.8 per 1,000 population in 1987, corresponding to 142,000 cases. Our studies suggest that as many as 29 percent of these, or 41,000 cases, may be due to NSAIDSs. We estimated a case fatality rate of 8 percent for persons age sixty-five and over hospitalized for peptic ulcer; given this, as many as 3,300 excess deaths possibly attributable to NSAIDs may occur each year. Since the average length-of-stay for peptic ulcer in elderly persons is 8.5 days, there may have been approximately 350,000 excess hospital days in 1987 due to NSAIDs.

Suggested Policy Directions

An increased knowledge of the frequency and cost of adverse drug reactions will enable both more rational therapeutic decisions by individual clinicians and more optimal social policy. Given quantitative information on medication risks, clinicians can change use of the drug (prescribe for fewer patients, use safer alternatives when available, and
use in lower doses for shorter duration) or can take measures to minimize side effects (prescribe prophylactic medications, increase monitoring for side effects, and intensify patient education). Policy changes that can result from better data on drug toxicities include withdrawal of drug from the market, change in drug labeling, and educational programs for physicians. In the long term, more precise estimates of the true costs associated with adverse drug reactions could stimulate development of prophylaxis and of alternative therapies. The need for timely and accurate drug safety data will become more acute as the number of diseases of the elderly that are managed with pharmacotherapy grows. For example, drug treatment of the common conditions of isolated systolic hypertension, benign prostatic hypertrophy, and osteoporosis is now imminent.

Careful epidemiologic studies that encompass large numbers of elderly drug users are required to obtain this information. This, in turn, calls for increased funding for geriatric drug epidemiology. Unfortunately, there is no coherent policy for such funding of these studies, which currently are supported by a variety of sources: FDA, the pharmaceutical industry, and other funding agencies.

FDA's primary mission with respect to pharmaceuticals is the licensing of new drugs. For postmarketing surveillance, its major focus is the spontaneous reporting system. Recent development efforts have made this system more comprehensive and capable of identifying possible adverse drug reactions more quickly. However, resources for controlled epidemiologic studies of adverse drug reactions are limited. The pharmaceutical industry supports some postmarketing surveillance studies. However, these are nearly always studies that bear upon FDA licensing or labeling decisions for recently marketed products. There are few incentives within the industry to fund other types of studies, no matter how compelling the public health issues.

Other funding comes from research agencies with an interest in specific adverse outcomes, such as the National Institutes of Health (NIH) and the Centers for Disease Control (CDC). Thus, NIH has funded study of drugs that can alter the risk of hip fractures, and CDC has investigated the link between L-tryptophan and the eosinophilia/myalgia syndrome. Within these agencies, drug studies must compete for the limited resources available for all other studies of these outcomes, a competition that has become more intense as constant dollar funding for federal research has decreased in the past decade. Unfortunately, epidemiologic drug studies rarely have high priority. Even for important questions of drug safety that can be addressed with relatively straightforward epidemiologic designs, years or even decades may pass before definitive studies are performed.
One relatively low-cost step that would facilitate study of adverse drug effects is to make databases collected for fiscal or regulatory purposes more suitable for drug epidemiology. These databases include Medicare and Medicaid files, state all-payer hospital discharge data sets, and data from health maintenance organizations (HMOs) and other organized systems for providing health care to defined populations. Databases are useful for drug epidemiology because they facilitate identification of cases of disease, selection of population controls, and ascertainment of drug exposure. Among the elderly, these tasks can be difficult and expensive to perform adequately with traditional interview-based methods.

Several steps could be taken to enhance the utility of databases for drug epidemiology. First, increased quality control for data collection to assure consistency, completeness, and accuracy is needed. This is particularly important for state Medicaid databases, which vary dramatically in content and quality. Provisions to computerize comprehensive data and assure research access also are needed. For example, until recently only a 5 percent sample of Medicare Part B physician claims were computerized by the Health Care Financing Administration (HCFA), which limited the usefulness of this database. If a national Medicare drug benefit were implemented, the resultant claims data would need to be computerized (possibly at a regional level), linkable with other Medicare data sets, and accessible for legitimate research. Some epidemiologic studies require access to pertinent medical records or to individual patients. The ensuing confidentiality questions can be resolved; for example, the Medicare Health Insurance Master File is now used routinely to select controls for epidemiologic studies.

Conclusion

Among persons age sixty-five or older, the medical and economic consequences of adverse drug reactions constitute a problem of considerable magnitude. However, data concerning the total frequency and costs of adverse drug reactions are rudimentary. Unfortunately, this ignorance impedes rational clinical and social decision making; we do not know how to adjust geriatric pharmacotherapy to minimize the consequences of adverse drug reactions. Because epidemiologic studies are required to provide reliable estimates of the incidence and costs of adverse drug reactions, there is a need to increase support for these studies, through both increased funding and enhancement of existing data resources. Increased allocation of resources to drug epidemiology has the potential to be cost-effective, as even a small decrease in adverse drug reactions could generate substantial savings in health care costs.
This research was supported in part by a grant (89-309-G) from The John A. Hartford Foundation and a cooperative agreement (FD-U-000073) with the U.S. Food and Drug Administration. In addition, Marie Griffin is a Burroughs Wellcome Scholar in pharmacoepidemiology.

NOTES

3. Baum et al., *Drug Utilization in the U.S.*
23. Griffin, unpublished data.
24. NCHS, “1987 Summary: National Hospital Discharge Survey.”