

Adverse drug reactions in the elderly

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ABSTRACT

Medications probably are the single most important health care technology in preventing illness, disability, and death in the geriatric population. Age-related changes in drug disposition and pharmacodynamic responses have significant clinical implications; increased use of a number of medications raises the risk that medicine-related problems may occur. The relationship between increased use of drugs including the prescription medication and elderly is well established. Majority of ADRs (80%) causing admission or occurring in hospital are type A reactions. Although less common occurring in elderly, type B ADRs may sometimes cause serious toxicity. Studies have correlated the integral association between old age and increased rate of adverse drug reactions arising out of confounding association between age and polypharmacy contributed by age-related changes in pharmacodynamics and pharmacokinetics at least for some medical conditions. A drug combination may sometimes cause synergistic toxicity which is greater than the sum of the risks of toxicity of either agent used alone. But, strategies to increase opportunities for identifying ADRs and related problems have not been emphasised in current international policy responses especially in India to the increase in elderly population and chronic conditions. Careful epidemiological studies that encompass large numbers of elderly drug users are required to obtain this information as increased knowledge of the frequency and cost of adverse drug reactions is important in enabling both more rational therapeutic decisions by individual clinicians and more optimal social policy.

Key words: Polypharmacy, elderly, drug safety data

BACKGROUND

Population aging is the process by which older individuals become a proportionally larger share of the total population. It was the most distinctive global demographic event that the world witnessed in the past century and is an important event for the twenty-first century too. It was initially experienced

by the more developed countries and has recently become apparent in the developing countries. Population aging will be faced globally by all countries in this century, although at varying levels of intensity and time.^[1] According to the World Health Organization (WHO), world's elderly population i.e., people 60 years of age and older is approximately 650 million at present and by 2050, it is forecast to reach 2 billion.^[2]

In 2008, five out of the top ten causes of mortality worldwide, other than injuries, were non-communicable diseases (NCDs) and expected to go up to seven out of ten by the year 2030. By then about 76% of the deaths in the world will be due to NCDs.^[3] Government and the WHO have already recognized the huge burden of preventable disease, disability, death and distress caused by the NCDs. The present international health agenda guided by WHO

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focuses on four conditions (cardiovascular disease, diabetes, cancer and chronic respiratory disease) responsible for most of the premature mortality and four 'lifestyle' risk factors (smoking, harmful alcohol use, lack of physical activity and high salt, high fat diets) leading to above conditions.^[4]

Medications play crucial role in geriatric health care as they treat chronic diseases, alleviate pain and improve quality of life.^[5] Age-related changes in drug disposition and pharmacodynamic responses have significant clinical implications, and increased use of a number of medications in elderly raises the risk of medicine-related problems that may occur.^[6] As medication use and the incidence of adverse drug outcomes increase with advancing age, it is important to ensure quality use of medicines in older people towards attaining a higher goal of healthy and active aging. But, use of drugs by the elderly and their clinical outcomes especially adverse drug reactions (ADRs) have not been prominent research topic and continues to be given low priority in National and International public health arena, at least in a developing country like India. However, we feel that this probably needs more attention in India because we have not completely dealt with the scourge of communicable diseases yet. We are now facing the additional burden of "graying" population and NCDs. In addition, 70% of all older people now live in low- or middle-income countries,^[2] including India where sustainable pharmacovigilance systems has not developed as yet.

We present here a discussion in ADRs and related problems on geriatric population.

EXTENT OF ADVERSE DRUG REACTION PROBLEM IN ELDERLY

The relationship between increased use of drugs and elderly is well established. Consequently, increased use of medications in elderly increases the risk of ADRs. Studies from around the world have shown a definite correlation between increasing age and ADR rate, at least for some medical conditions. Although very few such studies are available in Indian settings, Harugeri *et al.*^[7] in a hospital setting found that the prevalence of ADR-related hospital admissions was 5.9%, while in another such study^[8] in India, it was observed to be 6.7%. For India, Harugeri *et al.* predicted that 18000 bed days in a given time would be due to ADRs in elderly and total cost of hospital stay due to ADRs is estimated to be US \$4350 (INR 200100), that is US \$80.5 per patient (108.7% of per capita per year expenditure on health).

There has been much debate on whether advancing age by itself is a cause of increased risk of ADRs but merely a marker

for comorbidity, altered pharmacokinetics, and polypharmacy. Gurwitz and Avorn concluded that "patient-specific physiological and functional characteristics are probably more important than any chronological measure in predicting both adverse and beneficial outcomes associated with specific drug therapies",^[9] while studies around the world have clearly shown that the risks of ADRs (including interactions) is related to the number of medicines taken and sometimes due to inappropriate use of medicines. Carbonin *et al.* (1991)^[10] observed an exponential rather than the linear relation between the risks of ADR and the number of medicines taken in 9000 elderly Italian patients receiving 10 medicines. Review of several studies by Steward RB *et al.* found that the patients aged above 65 years use an average of two to six prescribed medications, and 1-3.4 non-prescribed medications. Out of all the factors that are most consistently associated with adverse drug reactions, polypharmacy is considered to be the most important.^[11] Thus, studies have correlated the integral association between old age and increased rate of ADRs arising out of confounding association between age and polypharmacy contributed by age-related changes in pharmacodynamics and pharmacokinetics at least for some medical conditions.

NATURE OF THE PROBLEM

The classical pharmacological classification of ADRs by Rawlins and Thompson^[12] divides ADR into two major subtypes: Type A reactions, which are dose-dependent and predictable, and unpredictable type B ('bizarre' or idiosyncratic) reactions. Majority of ADRs (80%) causing admission or occurring in hospital setting are type A reactions. They are predictable and potentially avoidable in nature as they are related to accentuation of known pharmacological effects of the drug. Drugs associated with type A reactions are generally with low therapeutic index and commonly used among elderly. The lists of medicines most likely to be used in the elderly include antibiotics, anticoagulants, digoxin, diuretics, hypoglycemic agents, antineoplastic agents and non-steroidal anti-inflammatory drugs (NSAIDs) and these are responsible for 60% of ADRs leading to hospital admission and 70% of ADRs occurring in hospital. Type B ADRs are usually uncommon, but rarely may sometimes cause serious toxicities.^[13] Therefore, ADRs in elderly are largely contributed by prescribing error e.g., large doses of drugs without taking into account, the effect of age and frailty on drug disposition, especially renal and hepatic clearance. The other contributing factor may be because of not considering the increased pharmacodynamic sensitivity of the elderly to several commonly used drugs, e.g., central nervous system and cardiovascular drugs.

Since only around 3000 subjects receive a medicine prior to

marketing, it is not surprising that less frequent (particularly type B) ADRs are often recognized only after marketing. The capacity of premarketing studies to recognize ADRs is further reduced by the limited numbers of patients in the age group of 65 or older in trials and that even smaller numbers of the oldest old. In addition, long latency diseases like cancer are difficult to detect on account of the short duration of study.

POLYPHARMACY AND ELDERLY

The terms, multiple medication use and polypharmacy are often used interchangeably. The latter has been defined in the literature in relative terms (for example, the administration of an excessive number of drugs) and in absolute terms, ranging from two to more than six simultaneous medications.^[14]

In contrast to general population, the incidence of combination therapy is found to be greatest in the elderly. A drug combination may sometimes cause synergistic toxicity, which is greater than the sum of the risks of toxicity of either agent used alone. For example, the combination of corticosteroids and NSAIDs: The risks of development of NSAID-induced peptic ulcer in older patients may increase by 10% among elderly.^[15] However, concurrent use of corticosteroids and NSAIDs had shown a risk of peptic ulcer disease that was 15 times greater than that of non-users of either drug.^[16] Similarly, the relative risk of hospitalization for hemorrhagic peptic ulcer disease in elderly patients (above 65 years) has been observed to be increased by manifolds on concurrent use of oral anticoagulants and NSAIDs, while the risks were lower when used alone.^[17] This suggests that there is certainly a need to recognize and consider the aspects of “synergism of toxicity” while prescribing medications in elderly. However, polypharmacy at times can effectively control certain disease condition e.g., hypertension and epilepsy.

STEPS OF MINIMIZING ADR IN ELDERLY

Altered pharmacokinetics and polypharmacy is largely unavoidable in many elderly patients. Respecting the individual needs of every individual patient is the preferred approach of prescribing in elderly. Some of the steps that may be helpful in minimizing ADRs in elderly may be:

- Maintaining accurate record of all medications in use: May include asking patients to bring all medications to clinic including the use of over-the-counter and complementary medicines.
- Number of medications (prescribed and non-prescribed):^[18] Monitoring to balance the need and avoid polypharmacy while minimizing under-use of vital drugs.
- Individual doses: Reducing the doses wherever appropriate and titrating them carefully from a low starting dose, if

pharmacodynamic sensitivity is likely to be the problem.

- Simple regimens of medication: Choose the preparation suitable for the patient and minimize the dose whenever needed, but avoid advising the patient to break a single tablet into two or three equal pieces.
- Ensuring safe management of medications by patients: Involving patients in decisions on their therapy by educating the patient about important side effects and what to do if they occur. Minimize hoarding of previously used and expired drugs.
- Therapeutic drug monitoring is encouraged,^[19] but should not replace clinical observation. Considering an ADR as a possible cause for any new problem.
- Utilizing available strategies and inter-disciplinary collaboration to enhance the quality use of medicines.

CONCLUSION

Drugs are double-edged weapons and increased use of drugs by elderly increases the risk of adverse drug reactions causing increased morbidity and mortality. In addition, economic consequences of ADRs constitute a problem of considerable magnitude. Developing countries have rapidly aging population and the governments are seeking guidance in promoting healthy and active aging. However, strategies to increase opportunities for identifying ADRs and related problems have not been emphasized in current policy responses in India to meet the increase in elderly population and chronic conditions. In addition, there is definite paucity of good quality research and data on ADRs in India. Further, growing pharmacotherapy with increase in the number of diseases in the elderly will require more timely and accurate drug safety data. Pharmacoepidemiological studies that encompass large numbers of elderly drug users are needed to obtain this information as increased knowledge of the frequency and cost of adverse drug reactions is important in enabling more rational therapeutic decisions by individual clinicians and more optimal social policy. Given quantitative information on medication risks, clinicians will be able to change the 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, educational programs to physician and changes in academic curriculum of pharmacology. This will result in promoting and ensuring a good health of older people, which can be of great benefit to their families and communities. In the long run, more precise estimates of the true costs associated with ADRs could stimulate development of prophylaxis and of alternative therapies.

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