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# Adverse drug reactions in elderly patients

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Many studies from around the world show a correlation between increasing age and adverse drug reaction (ADR) rate, at least for some medical conditions. More than 80% of ADRs causing admission or occurring in hospital are type A (dose-related) in nature, and thus predictable from the known pharmacology of the drug and therefore potentially avoidable. Frail elderly patients appear to be particularly at risk of ADRs and this group is also likely to be receiving several medicines. The toxicity of some drug combinations may sometimes be synergistic and be greater than the sum of the risks of toxicity of either agent used alone. In order to recognize and to prevent ADRs (including drug interactions), good communication is crucial, and prescribers should develop an effective therapeutic partnership with the patient and with fellow health professionals. Undergraduate and postgraduate education in evidence-based therapeutics is also vitally important. The use of computer-based decision support systems (CDSS) and electronic prescribing should be encouraged, and when problems do occur, health professionals need to be aware of their professional responsibility to report suspected adverse drug events (ADEs) and ADRs. 'Rational' or 'obligatory' polypharmacy is becoming a legitimate practice as increasing numbers of individuals live longer and the range of available therapeutic options for many medical conditions increases. The clear risk of ADRs in this situation should be considered in the context that dose-related failure of existing therapy to manage the condition adequately may be one of the most important reasons for admission of the elderly to hospital. Thus, age itself should not be used as a reason for withholding adequate doses of effective therapies.

## Extent of the problem

Adverse drug reactions (ADRs), including interactions, in older people are a common cause of admission to hospital [1, 2], are common in elderly patients in hospital [3], and are an important cause of morbidity and death. Even after excluding errors in drug administration, noncompliance, overdose, drug abuse, therapeutic failures, and possible ADRs, Lazarou *et al.* found the overall incidence of serious ADRs in the general hospitalized population of the USA to be 6.7% [4]. The incidence of fatal ADRs was 0.32% amongst patients from 39 prospective studies included in this meta-analysis [4]. Thus, ADRs are likely to be between the fourth and sixth leading cause of death in the USA [4]. The evidence quickly dispels any complacency or suggestion that this

problem is not an international one. An excellent systematic review by Wiffen *et al.* showed that the incidence of ADRs in European studies was around twice that in the USA, in those conducted either before or after an arbitrary cut-off date of 1985. In the more recent (post-1985) studies in the geriatric setting, the ADR rate for the USA and Europe studies was even greater (20%) than in studies carried out in general medicine settings [5]. Few would argue that this rate of ADRs is not a major public health problem. The Audit Commission has calculated that ADRs to medicines and medication errors cost the NHS £0.5 billion each year in longer stays in hospital [6]. Wiffen *et al.* used Department of Health statistics for 2000 to calculate that 38 000 admissions were due to ADRs in England alone, and that

ADRs were likely to have caused over 1.5 million extra bed-days, the equivalent of filling over 13 average-sized (400-bed) hospitals in 1 year [5].

There has been much debate on whether advancing age *per se* is a cause of increased risk of ADRs. 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’ [7]. Nursing home (generally frail) patients appear to be particularly vulnerable to ADRs. A prospective study of two nursing homes in Georgia found that >67% of 332 residents experienced probable ADRs [8]. ADRs were associated with polypharmacy, the mean number of drugs per patient in the ADR group being 7.8, compared with 3.3 amongst residents who did not experience them [8]. Other studies have also clearly shown that the risk of ADRs (including interactions) is related to the number of medicines taken [9–11], and that the elderly receive more medicines, sometimes inappropriately [12, 13]. Indeed, it is possible that the risk of ADRs is exponentially rather than linearly related to the number of medicines taken, and the ADR rate was 50% in 9000 mostly elderly Italian patients receiving 10 medicines [11]. Thus, many studies from around the world show a correlation between increasing age and ADR rate, at least for some medical conditions [14–16].

### Nature of the problem

It is also clear that more than 80% of ADRs causing admission or occurring in hospital are type A in nature [17]. Type A ADRs are dose related, an ‘accentuation’ of the known pharmacological effect of the drug, and thus predictable and potentially avoidable [18–22]. Antibiotics, anticoagulants, digoxin, diuretics, hypoglycaemic agents, antineoplastic agents and nonsteroidal anti-inflammatory drugs (NSAIDs) are responsible for 60% of ADRs leading to hospital admission and 70% of ADRs occurring in hospital [5]. Other cardiovascular medicines and analgesics are also important clinically [23]. These are generally drugs with a low therapeutic ratio (ratio between the average therapeutic and toxic dose). In addition, they all figure highly in lists of medicines most likely to be used in the elderly, and likely to be associated with adverse drug interactions. It has been suggested that type A ADRs are more common in the elderly and the unpredictable type B (‘bizarre’ or idiosyncratic reactions) less common [24]. However, some important and occasionally serious examples of type B toxicity (e.g. hepatotoxicity in association with the antibiotic flucloxacillin or the antibiotic combination,

coamoxiclav) appear to be commoner in elderly than younger individuals [25–27].

Frail elderly patients appear to be particularly at risk of ADRs. In some cases, this is because insufficient account is taken of the effect of age and frailty on the disposition of the drug, especially in relation to hepatic [28] and renal elimination [29], and too large a dose is prescribed. On other occasions, the increased pharmacodynamic sensitivity of the elderly to several commonly used drugs (particularly those affecting the cardiovascular and central nervous systems) is not taken into account when choosing the dose. These issues are all the more important because several diseases of these two systems, such as heart failure or epilepsy [30], are much commoner in the elderly. In addition, cardiovascular agents and anticoagulants are more likely than most other agents to cause ADRs that result in, or prolong hospital stay [10, 15].

The relationship between the number of medications taken and ADR risk has already been highlighted. Although around 10% of the general population take more than one prescribed medicine, the incidence of combination therapy is greatest in the elderly, in females, and in those who have had a recent hospital admission [31, 32]. A review of several studies indicated that patients aged >65 years use on average two to six prescribed medications, and 1–3.4 nonprescribed medications [33]. The potential dangers of what has been termed ‘polypharmacy’ have been known for some time [34] and indiscriminate polypharmacy has been identified as a major medical problem in some developing countries and a challenge for the World Health Organization’s action programme on essential drugs [35]. However, the recognition that several common conditions such as hypertension or epilepsy can only be adequately treated with more than one agent in a significant proportion of patients has led to the use of the terms ‘obligatory’ [36] or ‘rational’ polypharmacy. Nowhere is this a greater challenge than in the elderly population.

The toxicity of drug combinations may sometimes be synergistic and be greater than the sum of the risks of toxicity of either agent used alone. NSAIDs can increase the risk of peptic ulcer by around four-fold in patients aged  $\geq 65$  years [37]. The relative risk of the development of peptic ulcer disease among current users of oral corticosteroids (but not NSAIDs) was 1.1 (i.e. a 10% increase in risk) [38]. However, patients concurrently receiving corticosteroids and NSAIDs had a risk of peptic ulcer disease that was 15 times greater than that of nonusers of either drug [38]. Similarly, the relative risk of hospitalization for haemorrhagic peptic ulcer disease in patients aged  $\geq 65$  years receiving oral anticoagulants

compared with nonusers was 3.3 and for NSAID users, 2. However, compared with nonusers of either drug, the relative risk of haemorrhagic peptic ulcer disease among current users of both anticoagulants and NSAIDs was 12.7. Nevertheless, the prevalence of NSAID use among anticoagulant users was 13.5%, the same as in those who were not using anticoagulants [39], suggesting that this marked synergism of toxicity is still not widely recognized by prescribers.

### Recognition and reporting of ADRs

Although many type A ADRs are recognized during the drug development process and before licensing, this is not always the case, especially when they are uncommon or rare. In addition, the drug may be used off-label, sometimes at doses higher than those recommended. Even the initial manufacturers' recommended doses may be too high for some, particularly elderly individuals. The NSAID benoxaprofen was marketed in 1980. A year later, photosensitivity and serious hepatotoxicity (associated with 61 deaths in the UK) were reported in association with the drug and it was withdrawn in 1982. Only in 1982 were data published that indicated that withdrawal of the drug due to toxicity was necessary in 35% of 300 individuals taking the drug and in 69% of the 42 patients aged  $\geq 70$  years in one study. The authors concluded that the manufacturer's recommended dosage of 600 mg daily was associated with an unacceptable incidence of side-effects in the elderly [40]. 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. Nevertheless, delays in recognizing even these ADRs (e.g. the 20 years from initial marketing of flucloxacillin to the recognition of its hepatotoxic potential, particularly in the elderly) suggest that available postmarketing surveillance systems are not being used optimally. As a result, patients, including the elderly, may suffer unnecessarily.

### Avoidance of ADRs

Since most ADRs in the elderly are predictable and therefore potentially avoidable, good communication is pivotal in developing an effective therapeutic partnership with the patient and with fellow health professionals. Three hundred and twelve patients from the practices of five cardiologists and two internists who were returning for their routine follow-up visits in Boston were interviewed and discrepancies between medication bottles and medical records were present in 239 patients (76%). The 545 discrepancies in these patients were the result of patients taking medications that were

not recorded (51%); patients not taking a recorded medication (29%); and differences in dosage (20%) [41]. The age of the patient and his/her number of recorded medications were the two most significant predictors of medication discrepancy. This indicates that physicians should check medication lists with patients carefully (even obsessively) if ADRs and interactions are to be avoided, and illustrates that good communication is an essential prerequisite for rationalization of therapy [42]. This regular review process should continue, whether the elderly patient is in a hospital, nursing home or in the community, and a prescribing partnership between the prescriber, patient and other health professionals should be encouraged [43] so that good communication exists.

Whenever possible, the careful prescriber, faced with a choice, should choose the drug with the highest therapeutic ratio, provided efficacy is comparable. He/she should avoid combinations that exhibit additional or synergistic toxic effects (e.g. two substances with anticholinergic activity) [43]. Doses should be titrated up carefully from a low starting dose if pharmacokinetic or pharmacodynamic sensitivity are likely to be problems. In some cases, therapeutic monitoring of plasma drug concentrations (TDM) may be an adjunct to, but not a replacement for careful clinical observation [44]. The number of drugs prescribed should be kept to a minimum, and as few physicians [45] and dispensing pharmacies [46] as possible should be involved in the patient's care, since these measures have been shown to reduce the risk of receiving potential interacting drug combinations.

Physicians often look to their pharmacist colleagues for advice in relation to drug interactions. The ability of pharmacists at various stages of their training to identify potential drug interactions was studied by Weideman *et al.* [47]. Simulated medication profiles were created from a list of 16 drugs. The subjects detected only 66% of the interactions in the two-drug profiles, and 17% of the interactions in the 16-drug profile. None of the pharmacists in the study detected all interactions in the eight- or 16-drug profiles [47]. The only characteristic that correlated highly and positively with pharmacists' recognition of potential drug-drug interactions was the number of years since qualification [47]. Thus, experience (and training) appeared to be valuable. However, physicians with more experience were more likely to choose a longer- rather than shorter-acting benzodiazepine hypnotic for elderly people than those qualified more recently. This suggests that some prescribers select medicines out of habit rather than application of pharmacological principles [48]. In addition, physicians who

graduated from Canadian medical schools after 1989 were more likely to prescribe  $\beta$ -blocking drugs to elderly patients for secondary prevention after myocardial infarction than earlier graduates, so that important prescribing messages may not be getting through to doctors after they qualify [49]. There were also systematic differences between graduates of the different Canadian medical schools in this study. These findings indicate that the provision of good undergraduate education (ideally encompassing a core curriculum in clinical pharmacology) and continued professional development of graduate prescribers in evidence-based therapeutics are essential if old habits are to be replaced by new behaviour.

Even if all present and future prescribers (including nurses, pharmacists and other health professionals) are offered, and take up educational opportunities in therapeutics, it will still be difficult to keep completely abreast of this rapidly changing field, and one of the most important skills for the future will be to know where to find relevant and reliable information. Although 'to err is human', mistakes in prescribing or dispensing can cost lives. No pharmacist (even the most experienced) studied by Weideman and colleagues correctly recognized all the potential drug–drug interactions when presented with scenarios involving eight or more medicines [47]. The Audit Commission report has highlighted that many adverse drug events (ADEs, a broader definition than ADRs) are related to medication (e.g. prescribing or dispensing) errors. The US Agency for Healthcare Research and Quality (AHRQ) has also published a review of computer-based decision support systems (CDSS) to reduce prescribing errors [50] and the impact of CDSS has also been systematically reviewed [51]. Overall, these systems appear to reduce the numbers of ADEs. Wiffen *et al.* have reviewed the strengths and weaknesses of this approach, and outlined some examples of how decision support systems have promoted best practice [5]. The use of CDSS and electronic prescribing should be encouraged, but when problems do occur, the professional responsibility of health professionals to report suspected ADEs and ADRs to the relevant national bodies should continue to be highlighted.

The literature shows that elderly patients are exposed to more medicines and have an increased risk of type A (and of some type B) adverse reactions, and that many of these are avoidable. Knowledge of pharmacological principles and how ageing affects drug kinetics and response is essential if we are to promote safe prescribing. The occasional unavoidable occurrence of ADRs in the elderly should be set against the knowledge that

dose-related failure of existing therapy to manage the condition adequately may be one of the most important reasons for admission of the elderly to hospital [52]. Thus, age is not a reason for withholding effective therapies since, although the risk of death due to several common diseases (e.g. coronary heart disease, stroke, and cancer) is greater with increasing age, the proportional reduction in mortality is often as great or greater in the elderly than in younger people. The predicted percentage growth in the number of individuals aged 60 or more over the next 20 years varies from 20% in Italy to as high as 67% in Australia [53]. This continued world-wide expansion of the elderly population means that geriatric clinical pharmacology will continue to be an important area of research, and that the challenge to improve the risk–benefit ratio for existing and newly introduced medicines in the clinical setting should not be shirked. After all, the French composer Auber (1782–1871) once observed that despite its associated problems and shortcomings, he had come to the conclusion that 'ageing seems to be the only available way to live a long time'.

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