Clinical pharmacology in special populations: the extremes of age

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"Extrapolation of the results of studies performed predominantly in middle-aged adults to geriatric and pediatric patients, means that these vulnerable patients may be exposed to potentially ineffective therapies and unknown risks of adverse effects."

Patients at the extremes of age have been prescribed medicines without high quality evidence regarding safety and efficacy in the relevant populations for too long. Prescribing for geriatric and pediatric patients often involves extrapolating data obtained from clinical trials that predominantly include middle-aged adults with only one disease [1]. Ironically, information about the safety and efficacy of medicines for the most vulnerable patients, the frail elderly and the youngest of the pediatric age groups is especially scarce. The paucity of evidence in these populations can be partly attributed to practical and ethical issues in clinical trial design (e.g., large inter-individual variability, increased risk of adverse drug reactions and consent), regulatory requirements and economic factors. Building the evidence base to guide prescribing at the extremes of age requires research into new clinical trial designs and other methods for evaluating safety and effectiveness [2] as well as the support of drug regulatory bodies [3], funders of health research and the pharmaceutical industry.

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In drug-development trials, geriatric patients are usually excluded from Phase I studies owing to the higher risk of unanticipated toxicity. International guidelines on drug development now strongly recommend that Phase II and III studies should include older adults, including patients aged at least 75 years old, should not unnecessarily exclude patients with concomitant illness and, ideally, include patients representative of the population(s) that will be treated if the drug is licensed [4]. Regulatory agencies request information on the pharmacokinetics of a drug in people aged over 65 years and those with renal or hepatic impairment. However, as an increase in inter-individual variability is the predominant pharmacokinetic change with aging, screening tests on small numbers of older adults are unlikely to detect significant differences between different age groups. Pharmacodynamic studies in older people are only requested in specific circumstances and there is no requirement for clinical outcome data in geriatric patients to register or licence a drug for use in older adults.

Recent reforms by the US FDA and European Medicines Agency have provided new incentives and obligations for pharmaceutical companies to facilitate the development and licensing of medicines for the pediatric population [5–7]. There are now requirements, often with financial incentives, for manufacturers of new medicines to conduct pediatric studies if such medicines are likely to be useful in the pediatric population, so that new medicines can be licensed for use in children at the same time as in adults. Appropriate timing and sequencing of studies in relation to the adult drug-development plan needs careful contemplation when considering the balance of benefits versus risks

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for pediatric participants; the majority will be Phase II–III studies. Pediatric participation in Phase I studies is only considered ethically acceptable in particular circumstances, such as when there is no equivalent condition for initial study in adults, or in the treatment of a life-threatening disease with no or limited treatment options, and only if the potential benefits outweigh the potential risks for pediatric participants [8,9]. Public funding has also been made available to study off-patent medicines in children [6]. Similar provisions are not yet in place in many other regions, with consequent differences in licensing of pediatric-relevant medicines in different countries.

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Well-conducted Phase IV studies encompass the broad population of patients treated, including those at the extremes of age, and are important to detect rare adverse events and long-term effects of medications. Provisions for proactive risk management plans compel pharmaceutical companies to undertake postmarketing studies for registered indications. Special provisions are required for pharmacovigilance in children, in whom medications are often used off-label [7].

Observational studies provide important information for prescribing decisions in frail elderly patients and pediatric patients. Pharmacoepidemiology can assess patterns of medication use in large heterogeneous populations and help evaluate longer-term safety and effectiveness in the presence of issues that occur in real-world clinical settings (e.g., interacting drugs, suboptimal adherence and limited monitoring). These studies can measure important outcomes of therapy for patients at the extremes of age that may not be assessed in clinical trials. Clinical trial end points are often limited to surrogate markers, disease and mortality outcomes, which may have different implications at the extremes of age. For example, lowering low-density lipoprotein (LDL) cholesterol by 1.0 mmol/l is associated with a 56% decrease in ischemic heart disease events in 50 year olds, but only a 31% reduction in 70 year olds [10]. Even clinical events and death may be less meaningful to frail elderly individuals than functional outcomes. Pharmacoepidemiologic studies can correlate medication exposure with functional and quality-of-life measures, which may be more relevant to geriatric patients [11]. Observational studies can examine the outcomes of therapy over much longer time frames than the duration of most randomized trials, which is important to guide treatment decisions for older people who may have been prescribed many of their medications since middle age, and for children who may experience the effects of medications many decades after therapy. Although pharmacoepidemiologic studies have limitations, such as selection bias, misclassification of exposures and outcomes and confounding and logistic issues, better methods for addressing these problems are being developed [12].

Extrapolation of the results of studies performed predominantly in middle-aged adults to geriatric and pediatric patients means that these vulnerable patients may be exposed to potentially ineffective therapies and unknown risks of adverse effects. The principles used to extrapolate the evidence are similar in both populations. The dose is estimated using knowledge of pharmacokinetics at the extremes of age. The geriatric and pediatric populations cover wide age ranges (≥ 65 years and 0–18 years), with substantial differences in pharmacokinetics within the age groups. Studies in the appropriate age subgroups are needed to obtain meaningful data to inform treatment decisions for these populations. While pharmacokinetics in normal aging and development are reasonably well described in animal and human studies, there are very little data to describe the significant pharmacokinetic changes in frail elderly patients and sick premature neonates. Pharmacokinetics in frail elderly individuals are influenced by the loss of physiologic reserve, chronic inflammation, comorbidities and comedications (reviewed by [13]). Similarly, in neonates, there can be wide inter-individual variability related to gestational age, birth weight, postnatal age and comorbid conditions, such that even data from studies in well, term neonates may not be appropriate to extrapolate to sick, preterm neonates. Population pharmacokinetic studies may be used to identify, describe and measure the variability of pharmacokinetics in patients at the extremes of age.

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Estimates of drug effect also include changes in pharmacodynamics, which are less well defined than the pharmacokinetic changes at the extremes of age. Pharmacodynamic factors that influence drug efficacy and safety include the actions of the drug on its receptor, which, in many cases, is not well described at the extremes of age; the patient's overall physiology, particularly the diminished reserve of the very old and very young. Often, the underlying mechanisms for differences in efficacy and safety at the extremes of age are unknown or unpredictable, highlighting the need for appropriate evaluation of clinical outcomes in the relevant populations. The study of drug effects at the extremes of age may be challenged by differing patient capabilities (e.g., assessment of pain in older people with dementia or preverbal children requires appropriate validated tools) [14,15]. Some drug effects may be observed only in the pediatric population owing to the unique aspects of childhood (e.g., effects on growth and development) or because of diseases that only affect this population (e.g., neonatal respiratory distress syndrome). At the extremes of age, the therapeutic

index may be narrowed, or even less than one (e.g., in old-age sensitivity to the toxic anticholinergic effects of oxybutynin or tricyclic antidepressants may occur at lower concentrations than the therapeutic antispasmodic or antidepressant effects). The nature, severity and frequency of toxic drug effects may differ in the geriatric and pediatric populations [13,16]. Some adverse effects not observed in adults may only be seen when pediatric populations are exposed (e.g., chloramphenicol and the grey baby syndrome, and Reye's syndrome with aspirin) or occur at a greater frequency in children than in adults (e.g., serum sickness-like reactions with cefaclor).

It is difficult to practice evidence-based medicine when there is little or no evidence, but it is, perhaps, more difficult for clinicians to deny very old or very young patients a potentially beneficial therapy. Most medicines are, by default, licensed for use in geriatric patients but are not licensed for use in pediatric patients. In Australia, 28% of the government expenditure on pharmaceuticals in 2005–2006 was for patients aged 75 years and over [17], in whom there are often very few data on drug safety and efficacy. Only 2% of government expenditure on pharmaceuticals was for children under 15 years old [17]. However, between 40 and 90% [18] of prescribing in the pediatric population is for off-label use or for unlicensed medicines, with substantial clinical and financial costs to individuals and the community, which are not currently well captured by routinely collected data [19]. The practice of prescribing medicines for frail elderly adults and children in the absence of a good evidence base poses risks to our patients and removes any incentive for the proper evaluation of medicines for use in these populations. Patients at the extremes of age are vulnerable populations who have much to lose, as well as much to gain, from medical therapy. Clinicians need a strong evidence base through appropriately designed studies to guide therapy for these special populations. Innovative study design and regulations, as well as commitment from clinicians, researchers, government and the pharmaceutical industry will be required to optimize medication use for these patients.

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