COMMENTARY

Appraising clinical trial evidence for elderly people: special considerations

There are 116 scientific journals [1] and many websites dedicated to ageing, making it increasingly challenging for professionals caring for older people to select the most reliable information to apply to their practice.

Evidence is defined as clinically relevant research, from the basic sciences and especially from clinical trials of the efficacy and safety of therapeutic, rehabilitative and preventative regimens [2]. One of the key elements for the practice of evidence-based medicine is the appraisal of the validity, both internal and external, of the articles retrieved by searching the literature. Several useful publications on how to do this—as well as on how to apply the best evidence in clinical practice—are available [2–16].

The general principles for assessing the evidence are the same for any group of patients. However, older people present certain characteristics that, although not necessarily innate and unique to them, should be considered when appraising clinical trials dealing in old age.

Older people as a heterogeneous group

Elderly people are commonly excluded from clinical trials. Those who are included do not necessarily represent the spectrum of older patients we meet in clinical practice. When assessing clinical trials involving older people, it is important to look carefully at their profile, as they are a heterogeneous group. People aged 70 or less may be very different from those who are over 80, in terms of both social and physiological features and, consequently, in terms of treatment outcomes. Differences are likely to be encountered even among older patients within the same age group. Clinical trials with older people, therefore, should provide a detailed characterization of the patients and ideally look for individual determinants of outcome [17]. Apart from describing average results, it is important to mention those who did not respond to treatment, as well as those with adverse outcomes. This will better inform individual treatment decisions in clinical practice. Several papers have given practical advice on how to apply the results of trials and systematic reviews to the individual patient [18–20].

Older people as a group commonly presenting with multiple problems

Older people commonly present with multiple clinical and social problems. The first implication is the potential for confounding in clinical trials in old age. A example of this is the association between low blood pressure and increased mortality, which was observed in patients over 80. This association disappeared [21] when mortality rates were adjusted for potential confounders, including sex, physical function, cognitive performance, serum albumin concentration and heart disease.

The second point is that the multiple pathology commonly seen in older people predisposes to adverse effects with medication and non-compliance with research methodology. It may jeopardize the proper evaluation of treatment effects. The reasons for losses to follow-up need to be clearly described, since they may create an imbalance between the characteristics of individuals in the intervention and control groups, thus predisposing to the introduction of bias.

As a result of multiple medical problems, polypharmacy is common in elderly people. The pharmacodynamics and pharmacokinetics of a drug may be greatly modified in the context of polypharmacy, leading to unexpected effects and intolerance. Strict inclusion criteria are often used to overcome potential problems arising from polypathology and polypharmacy (i.e. to assure internal validity), but they limit the generalisability of the results to our patients.

Older people as a group presenting with problems that are difficult to define

Many conditions in old age are not easily defined and have no standard for correct diagnosis. The definition of a condition such as pneumonia is objective, since radiology can provide reliable criteria. However, the definition of Alzheimer’s disease or falls can be more complicated. The former, for instance, requires features from either the clinical history or the examination of scans which may provide at best a diagnosis of probable Alzheimer’s disease. Thus, when reading the results of clinical trials on elderly people we should consider the possibility of...
misclassification of cases, and determine if the measurement of outcomes involved the use of validated scales and instruments.

**Old age as a factor imposing special meaning for comparison groups**

Clinical trials assessing new drugs often use placebo groups as controls, as required by the licensing agencies. From a clinical perspective, it would be helpful if assessments of new drugs also compared them with existing treatments of choice. The limiting point of using solely placebo in the comparison groups is that it does not usually represent current practice. Even in situations where there is no treatment of choice, receiving formally administered inert treatment is not the same as waiting or doing nothing [22].

One issue arising from comparison groups involving older people is that these people sometimes receive poor care. As a result, trials on health services for elderly people that take current practice as a comparison are more likely to produce positive results [23]. Such trials giving positive interventions do not necessarily represent the optimum pattern of care to be delivered to old people.

**Ageing as a factor with effect on risk**

Relative risk is a measure of effect which may decline with increasing age. Explanations for this include the reduction in the number of susceptible older people (those more susceptible have already died), competing causes of death and disease, interactions between risk factors and age, high absolute levels of mortality at very high ages, and changes in the biological importance of a risk factor in disease initiation and progression at different ages [24]. On the other hand, the absolute risk attributable to the factor may increase in older age. Therefore, the association between a certain risk factor and outcome in old age might be underestimated if one considers the relative, rather than the absolute, risk. This could in part explain why the role of extrinsic factors, and the potential for prevention by the modification of these factors, have largely been overlooked in elderly subjects [25].

When reading an article on a certain treatment, one needs to look not only at the statistical significance of the results, but also their clinical significance. This may be assessed by the relative risk reduction. However, this may be limited as it does not consider the issue of baseline risk. This factor is particularly crucial in old age, when many conditions are highly prevalent (high baseline risk). To overcome this limitation, the calculation of the absolute risk reduction and its reciprocal, the number needed to treat, become mandatory.

By using the number needed to treat we may realise, contrary to what is commonly supposed, that interventions may have a greater impact on elderly than younger patients. Consider the treatment of hypertension in old age [26]. Antihypertensive treatment reduces the mortality in both younger or middle-aged adults and elderly subjects. The relative risk reduction is similar between the two groups, but the absolute benefit of treatment is more favourable in old age, as the number needed to treat for 5 years to prevent death and other cardiovascular events in younger and middle-aged patients is at least two times greater than that in elderly subjects.

**Conclusions**

The task of selecting the best evidence is central to evidence-based practice. It is particularly challenging in geriatric medicine because of two major factors: first, older people’s unfortunate exclusion from or under-representation in studies, and, second, the limitations of many clinical trials in dealing properly with common features and issues in old age. These factors highlight the importance of the geriatrician’s skills in carefully appraising the literature.

Since experimental conditions are often removed from everyday clinical practice, evidence from clinical trials or systematic reviews will always require integration with the context of individual patients, including their values, rights and preferences. This is particularly the case in geriatrics, given the heterogeneity of older people and the complex social and biological features that they typically present. To develop the ability effectively to accomplish such integration is an urgent task for us all.

**Key points**

- To practise evidence-based medicine, it is important to appraise the validity of articles retrieved from a literature search.
- Much information on old age has been published, making it an increasing challenge for professionals caring for older people to select the most reliable evidence for application to their practice.
- When appraising clinical trials relating to older people, we must consider those characteristics of old age which have important implications for the design, results and relevance of published studies.

**Acknowledgements**

This paper was written during the author’s attachment as a visiting fellow to the Department of Clinical
Geratology and Cochrane Dementia and Cognitive Impairment Group (http://www.jr2.ox.ac.uk/cdcig), Radcliffe Infirmary, University of Oxford, Oxford, UK. He acknowledges John Grimley Evans and Peter Smith for all the support received, as well as Alvaro Leite and Edmund T. Lonergan for their comments on the early version of this paper. J.M.C.F. has been sponsored by the Fundação CAPES, Ministerio da Educação, Brazil.

References

4. Oxman OD, Sackett DL, Guyatt GH. Users’ guides to the medical literature: II. How to use an article about therapy or prevention. A. Are the results of the study valid? JAMA 1993; 270: 2598–601.
5. Guyatt GH, Sackett DL, Cook DJ. Users’ guides to the medical literature: II. How to use an article about therapy or prevention. B. What were the results and will they help me caring for my patients? JAMA 1994; 271: 59–63.
12. Richardson WS, Detsky AS. Users’ guides to the medical literature. VII. How to use a clinical decision analysis. B. What were the results and will they help me caring for my patients? JAMA 1995; 273: 1610–13.